Time from last immunity event against infection during Omicron dominant period in Malaysia

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Highlights

- 45% of the vaccinated HCWs had COVID-19 during the Omicron period in Malaysia
- Vaccinated person with pre-omicron infection has lower risk for Omicron infection
- Immunity event of <90 days lowers Omicron risk, suggesting good timing for 4th dose
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Title

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Keywords: COVID-19, Omicron, hybrid immunity, prior SARS-CoV-2 infection, vaccination, healthcare workers, Malaysia

Running title: Previous infection and recent immunity event vs Omicron
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Abstract

We used a multi-centred, prospective cohort to study 482 two-dose and three-dose BNT162b2 vaccinated healthcare workers (HCWs) for SARS-CoV-2 infection during the Omicron dominant period in Malaysia. Between January 31\textsuperscript{st} and July 31\textsuperscript{st}, 2022, the cumulative incidence was 44.6\% (95\%CI 40.2 – 49.1\%) and the incidence rate was 3.33 (95\% CI 2.91-3.80) per 1000 person-days. Our study found that protection against Omicron infection was significantly higher for persons with previous SARS-CoV-2 infection (hazard ratio (HR) 0.41, 95\%CI 0.27 – 0.62) and persons with a more recent immunity event (<30 days [reference] vs >90 days, HR 3.82, 95\%CI 1.34 – 10.90) from the beginning of Omicron period.
Introduction

The SARS-CoV-2 Omicron variant (B.1.1.529) and its prominent sublineages continue to be the dominant (<98%) circulating strains globally since February 2022 [1–3]. The spike mutations of Omicron resulted in higher viral transmissibility and capability to escape neutralizing antibodies from vaccinated sera [4]. Immune evasion is evident as higher number of breakthrough and reinfection cases during the Omicron dominant period were observed [5,6]. Symptomatic COVID-19 cases increased as studies found moderate booster effectiveness against Omicron infection while the effectiveness against severe outcomes were largely preserved [7,8]. Almost three years into the pandemic, the population immunity landscape is widely heterogenous as people earned natural immunity from different SARS-CoV-2 variants and received various vaccine regimes across timeline. A growing number of epidemiological studies suggest that hybrid immunity (natural infection plus primary/booster vaccination) has an edge over infection-naïve vaccination-only persons against Omicron infection [9–13]. Laboratory studies found that immunity imprinting from a previous non-Omicron infection elicited stronger cross-reactive antibody and cell-mediated responses against Omicron infection [14,15]. However, the pressing policy question remains – what is the optimal 4th booster timing for those who have had a past infection, 3rd booster, and both? Here we used a cohort of 482 BNT162b2 vaccinated healthcare workers (HCWs) to evaluate the incidence rates of SARS-CoV-2 infection during the Omicron dominant period in Malaysia. Our primary objectives were to investigate if occupational exposures, booster vaccination, previous non-Omicron primary infection and, more importantly, recent immunity event can reduce the hazard of attaining an infection during the Omicron dominant period.
Methods

We used data from a multicentre, prospective cohort study. The study design are detailed in Supplement file and in our previous work [16]. Briefly, healthcare workers were prospectively followed up in scheduled visits for up to two years starting from the first vaccine dose. The vaccine used for primary and booster vaccination was BNT162b2. All vaccination dates and reverse transcriptase-polymerase chain reaction (RT-PCR) or antigen rapid test kit (RTK)-confirmed SARS-CoV-2 infections were recorded. In Malaysia, variant genotyping by whole genome sequencing were selective and limited to a small number of samples in the country. Therefore, we inferred the responsible variant by the period when the variant is dominating. Here, the Omicron incidence rate was analyzed from January 31, 2022 to July 31, 2022 as the Omicron dominant period in Malaysia was estimated to start from early February [2,3,8]. This period included the beginning and peak of BA.1/BA.2 Omicron wave and the beginning of BA.5 Omicron wave in Malaysia [3].

The outcome measure was any documented SARS-CoV-2 infection confirmed by RT-PCR or RTK that occurred in the Omicron period. The independent variables were booster vaccination, previous SARS-CoV-2 infection, and time from last immunity event. We used a 14-days lag time to convert one to “boosted” status, allowing vaccine effect to take place before measuring time-to-event [17]. We reported the cumulative incidence and incidence rates per 1000 person-days. Kaplan-Meier curve and risk table were shown as descriptive analysis. Cox-proportional hazard regression was used to estimate the association of the independent variables with infection. Age, sex, BMI and comorbidity status were used to adjust for the models. Schoenfeld’s global tests were used to test the proportional-hazards assumption. All data management and analysis were performed in R software version 4.2.1.
(the R Foundation for Statistical Computing) and Stata version 13 (Statacorp LP). A p-value less than 0.05 was deemed significant in all analyses.

**Results**

During the Omicron dominant period between January 31st and July 31st, 2022, the cumulative incidence of COVID-19 was 44.6% (95%CI 40.2 – 49.1%) in our HCW cohort and the incidence rate was 3.33 (95% CI 2.91-3.80) per 1000 person-days (Table 1). The majority (97.7%, n=210/215) of the infections were symptomatic, but do not require hospitalization. The incidence rates were not different by booster vaccination status. We observed that persons with a previous natural infection have 59% significantly lower risk for an infection during the Omicron period (HR 0.41, 95%CI 0.27 – 0.62, p<0.001) (Table 1, Figure 1).

However, despite having natural immunity from a previous infection, individuals whose last immunity event happened more than 90 days ago from Omicron period have the highest incidence rate and risk of Omicron infection compared to those with more recent immunity event (HR 3.82, 95%CI 1.34 – 10.90, p<0.012) (Table 1, Figure 1).

**Discussion**

The cumulative incidence of COVID-19 among HCWs is higher during the Omicron than delta wave (44.6% vs 10.0% [16]). This finding on HCWs is aligned with that of general population where Malaysia saw the highest peak of confirmed cases during Omicron wave [18]. HCWs’ risk of getting an Omicron infection was not associated with most of their occupational exposures, except for those performing nasopharyngeal swab procedure (HR 1.39, 95%CI 1.00-1.92) (Supplement Table 2). The minimized occupational hazards can be explained by more than 95% of the HCWs reported strict adherence to the recommended infection control protocols. This suggests that HCWs may have attained infection through community
transmission or workplace transmission during off duty activities. The finding on nasopharyngeal swab may be incidental or an indication that the highly transmissible (more replication in the upper respiratory tract) Omicron variant made swabbing procedure riskier than other procedures because of the proximity of HCWs to patient’s throat.

Individuals with past infection hybrid immunity have 59% significantly lower risk for COVID-19 during the Omicron dominant period in Malaysia compared to those who were vaccinated but remained infection-naïve. The primary infections of our cohort consists of 15 infections that predate two-dose vaccination (unable to ascertain strain but likely a mixture of ancestral or alpha by date proximity [3]) and 84 breakthrough infections that occurred during Delta dominant period. Our result mapped closely with findings that showed previous pre-Omicron infection provided 44 – 50% protective effectiveness against symptomatic Omicron infection [9,10,19]. The reduced risk of Omicron infection can be explained by more durable SARS-CoV-2 anti-spike IgG titre levels among individuals with hybrid immunity than those without (Supplement table 3) and that the sera of delta infected individuals have better neutralization capacity against Omicron epitopes than sera of infection-naïve individuals [20]. Our study showed no significant interaction between past infection and booster status, supportive of a Qatari study which suggests that the protection from natural and vaccine-induced immunity acted independently rather than in synergy [9].

Overall, individuals with an infection from previous variants of concern (VOCs) produce more robust humoral response than infection-naïve individuals. This suggests beneficial immune imprinting and cross-reactivity immunity against Omicron infection.

It is counterintuitive to find no discernible difference in infection risk between the boosted and unboosted individuals in our study. This is likely due to the high booster vaccination rate
(95%) among our participants. We assessed and confirmed that when vaccination and natural infection were consolidated as an “immunity event” that happened sequentially, the protection against infection (Table 1) and IgG antibody (Supplement table 3) waned with time. The majority in our cohort, including those who had Delta infection, received booster vaccination from November to December 2021, which was approximately 60-90 days before the start of Omicron period in Malaysia. Immunity event older than 90 days from the start of Omicron wave yielded significantly higher risk for Omicron infection. Despite past infection conferring moderate protection against Omicron, the protection weakened if not for a recent booster. This implies that facing the threats of an upcoming variant, a vaccination update is beneficial even for individuals with previous infection; the optimal time for the subsequent booster update is when the latest immunity event is more than 90 days ago from start of new variant period. This suggestion is based on the protection against infection parameter. For a wider booster policy recommendation, we should consider other public health benefits such as protection against severe outcomes and cost effectiveness.

This study has several strengths. As opposed to studies reported vaccine effectiveness against infection during the early phase of Omicron and excluded individuals with natural immunity, our study covered the entire peak period of Omicron to better estimate the incidence rate of individuals with and without natural immunity. Our second strength is the prospective cohort design. We started with a homogenous group and conducted periodical checks on individual’s serology, exposure, and infection history. The individual serology data is useful in supporting observations from infection data, where this is not easily achievable in population research. Cohort design also allowed us to calculate incidence per person-time, besides crude incidence. Our main limitation is that the variant deduction is based on date proximity to strain domination period instead of genotyping as genotype tests was limited
to administrative genomic surveillance. Another caveat is that while our study findings can be generalized to the 18–59-year-old, healthy general population, the findings may not be extrapolated to older age groups and immunocompromised populations. Lastly, at the time of writing, a new recombinant Omicron sublineage, XBB, emerged and caused a surge in breakthrough and reinfection in Malaysia’s neighbouring country, Singapore [21]. The immune escape potential of XBB is still under investigation and our result may need careful generalization to this latest Omicron sublineage until more data is available.

Conclusion

Pre-Omicron natural infection is associated with significantly lower risk for symptomatic infection among the two-dose or three-dose vaccinated HCWs during the Omicron dominant period in Malaysia. Nevertheless, updating breakthrough infection immunity with a booster vaccination can enhance protection. The recommended timing for subsequent booster update is when the last immunity event was more than 90 days ago from the start of new variant wave.

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Conflict of Interest

All authors declare no conflict of interest.

Ethical Approval Statement

The study was approved by the Medical Research and Ethics Committee (MREC) Ministry of Health Malaysia and registered (NMRR-21-56-58212).

Funding Source

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Data Availability

The dataset analyzed for the current study is available from the corresponding author upon reasonable request.

Contribution

Peariasamy, Yang, Lee and Koh conceptualized and designed the study. Yang, Lee, Koh, Abdul Rahim, Gokilavanans, Mohamed, Sevalingam, Yen and Chand collected data. Yang conducted statistical analysis. Yang, Mat Ripen, Peariasamy, Lee and Koh interpreted the data. Yang drafted the manuscript. All authors were involved in critical revision of the manuscript for intellectual content and approved of the final version for submission. Yang and Mat Ripen obtained funding. Peariasamy provided supervision in this study.
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Figure 1. Kaplan-Meier curve of cumulative incidence probability by pre-Omicron natural infection and time since last immunity event.
Table 1. Incidence rates and adjusted hazard ratio of infection during Omicron dominant period, stratified by booster, pre-Omicron natural infection and time since last immunity event.

<table>
<thead>
<tr>
<th></th>
<th>Population</th>
<th>Person-days</th>
<th>Case</th>
<th>Incidence rate per 1000 person-days (95% CI)</th>
<th>Adjusted hazard ratio, aHR (95% CI)</th>
<th>P value for aHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>482</td>
<td>64,609</td>
<td>215</td>
<td>3.33 (2.91 - 3.80)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Booster dose (3rd dose vaccine)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>2,521</td>
<td>12</td>
<td>4.76 (2.70 - 8.38)</td>
<td>(ref)</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>461</td>
<td>62,088</td>
<td>203</td>
<td>3.27 (2.85 - 3.75)</td>
<td>0.66 (0.37 - 1.19)</td>
<td>0.168</td>
</tr>
<tr>
<td><strong>Pre-Omicron natural infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>384</td>
<td>48,230</td>
<td>191</td>
<td>3.96 (3.44 - 4.56)</td>
<td>(ref)</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>98</td>
<td>16,379</td>
<td>24</td>
<td>1.47 (1.00 - 2.19)</td>
<td>0.41 (0.27 - 0.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Time since last immunity event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 days</td>
<td>23</td>
<td>3,903</td>
<td>5</td>
<td>1.28 (0.53 - 3.08)</td>
<td>(ref)</td>
<td>-</td>
</tr>
<tr>
<td>30-60 days</td>
<td>37</td>
<td>5,567</td>
<td>13</td>
<td>2.34 (1.36 - 4.02)</td>
<td>1.87 (0.66 - 5.28)</td>
<td>0.236</td>
</tr>
<tr>
<td>60-90 days</td>
<td>399</td>
<td>52,552</td>
<td>184</td>
<td>3.50 (3.03 - 4.05)</td>
<td>2.61 (1.07 - 6.41)</td>
<td>0.035</td>
</tr>
<tr>
<td>&gt; 90 days</td>
<td>23</td>
<td>2,587</td>
<td>13</td>
<td>5.03 (2.92 - 8.65)</td>
<td>3.82 (1.34 - 10.90)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Hazard ratios are adjusted for age, body mass index, sex and presence of comorbidity.