Comparative effectiveness of BNT162b2 and mRNA-1273 booster dose after BNT162b2 primary vaccination against the Omicron variants: A retrospective cohort study using large-scale population-based registries in Japan

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Running title: Heterologous booster against COVID-19

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Abstract

Background: Direct comparative effectiveness of booster doses of BNT162b2 and mRNA-1273 after BNT162b2 primary vaccination is unknown.

Methods: We investigated comparative effectiveness of BNT162b2 and mRNA-1273 booster dose using data from registry systems for vaccination and COVID-19 infection in a local city in Japan. We followed participants aged ≥16 years who completed the BNT162b2 primary vaccination between November 22, 2021, and April 15, 2022. We collected information on age, sex, vaccination status, vaccine type, and infection status. Age was categorized as 16–44, 45–64, 65–84, and ≥85 years. Vaccine effectiveness for mRNA-1273 and no booster vaccination against BNT162b2 was estimated using age-stratified Cox regression adjusted for age, sex, and days since the second vaccination. The estimated hazard ratios for mRNA-1273 and no booster vaccinations were integrated separately using random effects meta-analyses.

Results: During the study period, we identified 62,586 (40.4%), 51,490 (33.2%), and 40,849 (26.4%) participants who received BNT162b2, mRNA-1273, and no booster dose, respectively. The median age was 69, 71, and 47 years for BNT162b2, mRNA-1273, and no booster dose, respectively. The integrated hazard ratio with reference to BNT162b2 was

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1.72 for no booster vaccination and 0.62 for mRNA-1273. The comparative effectiveness of mRNA-1273 was similar across age categories.

Conclusions: Both homologous and heterologous vaccinations are effective against Omicron variants. In the head-to-head comparison, the effect was stronger in people who received heterologous vaccination than in those who received homologous vaccination. These findings may help improve logistics and decision making in future vaccination programs.

Keywords: Omicron variants, BNT162b2, mRNA-1273, booster dose, population-based registries

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Introduction

Previous studies reported acceptable safety profiles and sufficient levels of antibodies after the booster dose of coronavirus disease (COVID-19) vaccines [1,2]. These studies showed that the levels of IgG anti-SARS-CoV-2-binding antibody and neutralizing antibody differed by the combination of booster vaccine and primary course. Noticeably, participants who received heterologous mRNA-1273 (Moderna) booster dose after two primary doses of BNT162b2 (Pfizer-BioNTech) showed higher antibody levels than those with three homologous BNT162b2 doses.

Higher antibody levels are inversely associated with symptomatic COVID-19 [3,4]. However, the actual effectiveness of heterologous and homologous vaccination has not been directly compared at the population level. A recent population level study in the UK examined the effectiveness of several combinations of primary course and booster dose [5]. The study found that BNT162b2 or mRNA-1273 booster vaccination after BNT162b2 primary course effectively protected the participants against COVID-19 when compared to no booster dose. Although mRNA-1273 booster vaccination after the BNT162b2 primary course showed higher vaccine effectiveness than the three doses of BNT162b2 vaccines,

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the two vaccines were not directly compared because that study aimed to estimate the vaccine effectiveness compared with no booster dose.

In Japan, BNT162b2 or half dose (50 μg) of mRNA-1273 has been available as a booster dose since December 1, 2021, for people aged ≥18 years, regardless of the type of primary vaccine course. The effectiveness of vaccines should be fully notified, especially when there is a choice of booster vaccine, as in many countries. In addition to individual choice, this information is useful for future logistics in vaccination campaigns. We therefore conducted a head-to-head comparison of vaccine effectiveness between BNT162b2 and mRNA-1273 in people who completed the primary BNT162b2 vaccination course in Japan using data from registry systems for vaccination and COVID-19.

Methods

Data source

We used vaccination records linked with the Health Center Real-time information-sharing System on COVID-19 (HER-SYS) data [6], collected between February 19, 2021, and April 15, 2022, in Shimonoseki City, a municipality located in the southwestern region of Japan. Briefly, Shimonoseki has approximately 250,000 residents and 130,000 households

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in an area of 716 sq. km. in 2022 [7]. There are 26 hospitals with 5,300 beds, and the population per physician is approximately 350 [8].

The vaccination records contain information on all residents of Shimonoseki city, including age, sex, number of doses (first, second, and booster) of COVID-19 vaccine, date of vaccination, and type of vaccine (BNT162b2, mRNA-1273, and ChAdOx1-S [Oxford/AstraZeneca] that were available in Japan during the study period). As of April 11, 2022, approximately 80% of the residents of Shimonoseki city completed two primary doses of the COVID-19 immunization course, and approximately 50% received a booster dose [9].

The HER-SYS was established to share information on patients with COVID-19 in governments, community health centers, and medical facilities. Patients diagnosed with COVID-19 and their close contacts were registered in the HER-SYS for monitoring and health management. The HER-SYS data includes the date of report on COVID-19 diagnosis, date of hospital admission for COVID-19, and date of death from COVID-19. The date of diagnosis in the HER-SYS was entered by a physician for patients with definitive diagnosis of COVID-19, which was made by the physician based on the results of polymerase chain reaction and/or antigen testing [10,11]. People who tested positive

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outside the medical facilities still required physician's assessment to be registered as infected cases during the study period. Although the HER-SYS was designed to collect other clinically important information, such as symptoms of COVID-19, comorbidities, smoking, and body mass index, we were unable to utilize the information because of missing values, as input of details was not mandatory at the time of the study.

The vaccination records were linked to the HER-SYS data via the Basic Resident Register of Shimonoseki City using anonymized ID created based on name, sex, and date of birth. Almost all (i.e., 99.98%) vaccination records and 76.3% of HER-SYS data were linked to the Basic Resident Register. All HER-SYS data linked to the Basic Resident Register were linked with the vaccination records. The linkage rate of the HER-SYS data with the Basic Resident Register was relatively low because the data included information on some people who were diagnosed with COVID-19 at medical institutions in Shimonoseki City but lived outside the city.

The study was approved by the Institutional Review Board of the University of Tokyo (2021187NI-[3]) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. As our analyses involved a secondary use of anonymized data that was routinely collected by the local government in Japan, the

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requirement for individual informed consent was waived in accordance with the current ethical guidelines for medical and health research involving human participants in Japan.

Participants

Of the study population vaccinated with the primary course, >80% received two doses of BNT162b2, while the others received two doses of mRNA-1273, heterologous vaccination, or unknown type of vaccination as a primary course. We included Shimonoseki residents aged ≥16 years and who had completed two primary doses of the BNT162b2 COVID-19 immunization course by November 22, 2021—the start of the sixth wave of COVID-19 in Japan. We excluded participants who received ChAdOx1-S (AstraZeneca) as a booster dose, and those who had already been diagnosed with COVID-19 by the start of the sixth wave.

Variables

The primary outcome was COVID-19 diagnosis, defined as availability of a diagnosis date in the HER-SYS data between November 22, 2021 and April 15, 2022, when Omicron variants predominantly circulated. The other outcomes were hospitalization and COVID-

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19-related death, defined as availability of a date for these events in the HER-SYS data, although we failed to conduct statistical adjustment for these outcomes due to their rarity. The exposures were as follows: (i) receiving mRNA-1273 as a booster dose (heterologous COVID-19 vaccination) and (ii) receiving no third dose. The effects of these exposures were estimated with reference to receiving BNT162b2 as the booster dose (homologous COVID-19 vaccination). In the mass vaccination program, those who completed the primary COVID-19 vaccination course at least 6 months prior were eligible for the booster dose [12]. For people aged ≥18 years, BNT162b2 or half dose (50 μg) of mRNA-1273 was available as a booster dose regardless of the type of primary vaccine course, while only BNT162b2 was available as a third dose for people aged ≤17 years.

The exposures were treated as time-dependent variables in the analyses, and the vaccination status was changed from "no booster" to "vaccinated with BNT162b2 booster" or "vaccinated with mRNA booster" seven days after the booster dose was administered. For a sensitivity analysis, the time-dependent exposure was further divided based on the time from the booster dose (post-booster week 2−6, 7−12, and 13−). The thresholds of post-booster week category were set based on the half of maximum follow-up day, the maximum follow-up day, and beyond in those with mRNA booster. Other variables used

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for statistical adjustment were age, sex, and number of days from the second dose to the start of the sixth wave. Age was categorized as 16–44, 45–64, 65–84, and ≥85 years for stratified analyses.

Statistical analyses

We described the characteristics of the participants stratified according to vaccination status at the end of the follow-up period. The effect of the booster COVID-19 vaccination dose on infection was analyzed for each age category using Cox regression with time-dependent exposures. We followed participants from November 22, 2021, the start of the sixth wave, to the date of infection, the date of death from COVID-19, or April 15, 2022, whichever occurred first. Death from other reasons and moving out of the city (i.e., out of the cohort) were disregarded because such data were unavailable. The results of the regression analyses for each category were integrated using a random effects meta-analysis. Integration was performed for heterologous vaccination and for no vaccine separately, with homologous vaccination as a reference category for both. Heterogeneity among age categories was assessed using I^2 measure [13]. To account for time difference from the booster dose (i.e., waning) between the groups, we conducted a sensitivity analysis for the entire cohort using

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Cox regression with time-dependent exposure further divided by post-booster week category (post-booster week 2−6, 7−12, and 13−). The other variables included in the model were age, sex, and number of days from the second dose to the start of the sixth wave, as in the main analysis. With BNT162b2 post-booster week 2−6 as a reference, we presented the hazard ratio (HR) for each exposure category. Statistical analyses were conducted using R Statistical Software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 259,361 residents of Shimonoseki City, we identified 258,234 participants aged ≥16 years and who had completed two primary doses of BNT162b2 by November 22, 2021 (**Supplementary Figure 1**). We excluded 3 participants who received ChAdOx1-S as a booster dose and 1,124 participants who had already been diagnosed with COVID-19 by the start of the sixth wave. Of the remaining 154,925 participants, 62,586 (40.4%) received BNT162b2, 51,490 (33.2%) received mRNA-1273, and 40,849 (26.4%) received no vaccine as a booster dose by the end of the follow-up period. The distribution of age categories and days from the second dose to the start of the sixth wave were similar in the

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BNT162b2 and mRNA-1273 groups, while participants without booster doses were much younger and had fewer days from the second dose to the start of the sixth wave than those in the other two groups (**Table 1**). The duration (mean [standard deviation] days) from the start of the sixth wave to the administration of BNT162b2 booster was shorter than that of mRNA-1273 (96 [31] vs. 103 [16] days) (**Table 1**). The number of COVID-19 cases and the number of booster dose administration in the cohort are shown in **Figure 1**. The maximum follow-up days after the booster dose were 133 for those with BNT162b booster and 80 for those with mRNA-1273 booster. Comparison of no vaccination with homologous vaccination showed that the proportions of infection (4.9% vs. 1.4%) and hospitalization (0.3% vs. 0.1%) for COVID-19 were higher in participants with no vaccination (Table 2). Further, participants who received mRNA-1273 were less likely to be diagnosed with COVID-19 than those who received BNT162b2 (0.7% vs. 1.4%).

After adjusting for age, sex, and days from the second dose to the start of the sixth wave, the risk of infection was higher in participants without a booster dose than in those with a BNT162b2 booster dose across all age categories (**Figure 2A**). The integrated results showed that participants without a booster COVID-19 vaccine dose were more likely to be infected (HR: 1.72, 95% confidence interval [CI]: 1.22–2.22, I^2 = 80%) than participants

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with BNT162b2 booster dose. In contrast, participants with the mRNA-1273 booster (i.e., heterologous vaccination) dose had a lower risk of COVID-19 than those with BNT162b2 booster (i.e., homologous vaccination) dose (HR: 0.62, 95% CI: 0.50–0.74, I^2 = 0%) (**Figure 2B**). The effects of heterologous vaccination were consistent across all age categories. In the sensitivity analysis that accounted for time from the booster dose, those with heterologous vaccination had consistently lower risk of COVID-19 over time than those with homologous vaccination (HR: 0.61, 95% CI: 0.49–0.7 for post-booster week 2−6) (**Table 3**). Although the effect of homologous vaccination waned over time, those with BNT162b2 booster had lower risk of COVID-19 than those without the booster dose throughout the follow-up period.

Discussion

To the best of our knowledge, this is the first study to compare the effectiveness of heterologous vaccination (mRNA-1273 after two doses of BNT162b2) and homologous vaccination (three doses of BNT162b2), directly. The registry systems for vaccination and infection, a relatively homogenous primary vaccination strategy, and the availability of two different mRNA booster doses in Japan allowed a large-scale direct comparison of

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vaccination regimens. While homologous vaccination was associated with less risk of COVID-19 than no booster dose, heterologous vaccination had an even more protective effect against COVID-19 than homologous vaccination.

Previous studies indicated that heterologous vaccination may have a greater protective effect than homologous vaccination based on neutralizing antibody response [1,2]. The IgG serum binding antibody and pseudovirus neutralizing antibody were higher in participants who received mRNA-1273 booster dose after two doses of BNT162b2 than in those who received three doses of BNT162b2 [1]. Later, a study from the UK confirmed that the effectiveness of heterologous vaccination was indeed higher than that of the homologous vaccination at the population level. However, these studies used no booster vaccination as a reference and did not conduct direct comparisons between heterologous and homologous vaccinations. The present study directly compared two mRNA booster vaccination regimens and suggested that heterologous vaccination was more effective against infections by Omicron variants than homologous vaccination at the population level. Informing the population about the better vaccine effectiveness of the mRNA-1273 booster dose than BNT162b2 may further help in individual decision-making for COVID-19 vaccination.

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Heterologous booster vaccination has also attracted the attention of the world to optimize logistics under an ongoing global inequity in vaccine distribution [14]. Despite the accumulating evidence of the safety and effectiveness for homologous vaccination [15–17], comparative effectiveness of heterologous vaccination remains uncertain. Nonetheless, many countries have adopted heterologous booster regimens to respond to the surge of new variants [18–21]. Because of a safety profile similar to that of homologous vaccination[1,2] and the higher effectiveness confirmed by the present study, heterologous vaccination could be a viable option for many countries. The booster dose in general reinforces protection against COVID-19[5]; thus, an indiscriminative promotion of homologous and heterologous booster dose in vaccination campaigns may further contribute to protecting people from COVID-19.

This study has several limitations. First, the generalizability of the results may be limited because the current study was conducted at a local municipality in Japan, where almost all residents were Japanese. The effects of heterologous vaccination may differ in other races. In addition, most of the viruses circulating during the study period were Omicron variants [22]. Thus, the effects of the third dose of COVID-19 vaccine may differ for other or future variants. Second, information on the participants was limited. We were

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unable to adjust for known risk factors for COVID-19, such as comorbidities, smoking, and body mass index, due to the lack of data. Imbalance of these factors between the groups may have led to biased results in either direction depending on their distributions. Similarly, we were unable to control for healthcare seeking behavior and access to healthcare. The comparative effectiveness of homologous vaccination against no booster vaccination may have been underestimated if those without booster dose did not seek healthcare for COVID-19. Moreover, we were unable to censor the participants who died of causes other than COVID-19 and those who moved out of the municipality due to the lack of data. According to the census of Shimonoseki City, the number of individuals aged ≥15 years decreased by 1,663 between the end of November 2021 and end of April 2022 [7]. The results of comparison, especially between homologous vaccination and no vaccination, may have been affected by a lack of proper censoring. However, we hypothesize that the results of the comparison between homologous and heterologous vaccinations are still meaningful due to the absence of a reason to claim that censoring occurred disproportionately between the two groups. To optimize vaccination program, future studies are warranted to compare effectiveness of several existing regimens of COVID-19 vaccines while addressing these concerns.

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In conclusion, two different types of mRNA booster doses after two primary doses of the BNT162b2 COVID-19 immunization course were associated with a lower risk of COVID-19. In the head-to-head comparison, the protective effect against infection was stronger with heterologous vaccination than with homologous vaccination. This information can be utilized for individual decision-making in future vaccination campaigns. Moreover, policymakers should consider heterologous mRNA vaccination as a viable option, along with homologous vaccination, to protect people from COVID-19.

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NOTES

Author contributions

SO, NM, and H Yasunaga conceived and designed the study. SO, MN, and H Yasunaga were responsible for data acquisition. SO and NM analyzed data. All authors interpreted data. SO wrote the first draft of the manuscript. All authors reviewed and edited the manuscript critically for important intellectual content. All authors approved the final draft of the manuscript.

Ethical considerations

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, University of Tokyo (approval no. 2021187NI-[3]). As our analyses involved a secondary use of anonymized data that was routinely collected by the local government in Japan, the requirement for individual informed consent was waived in accordance with the current ethical guidelines for medical and health research involving human participants in Japan.

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Data availability statement

The database used in this study was maintained by Shimonoseki city, Japan. Restrictions applied to the availability of data that were used with permission for this study. Therefore, data are not publicly available.

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Conflict of interest

SO is a member of the Department of Eat-loss Medicine, a cooperative program between the University of Tokyo and ITO EN Ltd and received grants from the Ministry of Health, Labour, and Welfare, Japan, and the Ministry of Education, Culture, Sports, Science and Technology, Japan, outside the submitted work. NM, H Yamana, and TJ are member of the Department of Health Services Research, a cooperative program between the University of Tokyo and Tsumura. TJ and H Yasunaga received grants from the Ministry of Health, Labour, and Welfare, Japan, and the Ministry of Education, Culture, Sports, Science and

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Technology, Japan, outside the submitted work. YO reports grants or contracts from Japan Medical Education Foundation (https://www.jmef.or.jp/). The other authors report no potential conflicts of interest.

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Table 1. Characteristics of participants in each regimen

Characteristics	Booster dose		
	BNT162b2	**mRNA-1273**	**None**
n	62,586	51,490	40,849
Female, n (%)	39,200 (62.6)	29,149 (56.6)	22,019 (53.9)
Age, years, median (IQR)	69 (55–78)	71 (62–79)	47 (34–61)
Age category, n (%)			
16–44	8,649 (13.8)	3,694 (7.2)	17,814 (43.6)
45–64	15,400 (24.6)	12,160 (23.6)	14,279 (35.0)
65–84	31,080 (49.7)	29,429 (57.2)	5,935 (14.5)
≥85	7,457 (11.9)	6,207 (12.1)	2,821 (6.9)
Days from the second dose to the start of wave 6, mean (SD)	135 (39)	121 (21)	70 (43)
Days from the start of wave 6 to booster dose, mean (SD)	96 (31)	103 (16)	—

IQR, interquartile range; SD, standard deviation

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Table 2. Unadjusted outcomes in each regimen

Outcomes	**Booster dose**		
	BNT162b2	**mRNA-1273**	**None**
n	62,586	51,490	40,849
Infection, n (%)	863 (1.4)	376 (0.7)	1,990 (4.9)
Hospitalization, n (%)	84 (0.1)	33 (0.1)	122 (0.3)
Death, n (%)	0 (0.0)	1 (0.0)	9 (0.0)

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Table 3. The risk of COVID-19 for each post-booster week category with reference to 2–6 week category in BNT162b2 group.

Booster	Post-booster week category	Hazard ratio [95% CI]
No booster		1.82 [1.57, 2.11]
BNT162b2	WEEK 2−6	Reference
BNT162b2	WEEK 7−12	1.52 [1.27, 1.83]
BNT162b2	WEEK 13−*	1.22 [0.93, 1.60]
mRNA-1273	WEEK 2−6	0.61 [0.49, 0.76]
mRNA-1273	WEEK 7−12**	0.69 [0.45, 1.04]
mRNA-1273	WEEK 13−	−

* Maximum follow-up days after BNT162b booster was 133

** Maximum follow-up days after mRNA-1273 booster was 80

The hazard ratio for each category was estimated by Cox regression, adjusted for age, sex, and number of days from the second dose to the start of the sixth wave of COVID-19. Abbreviation: CI, confidence interval; COVID-19, coronavirus disease.

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Figure Legends

Figure 1. Time from the start of sixth wave to COVID-19 diagnosis and booster dose. Panel A shows the number of COVID-19 cases at each time point. Panel B shows the number of booster dose administration at each time point.

Abbreviation: COVID-19, coronavirus disease

Figure 2. The risk of COVID-19 for no booster dose group and for mRNA-1273 booster group with reference to BNT162b2 booster group.

Panel A shows the risk of COVID-19 for no booster group with reference to BNT162b2 booster group. Panel B shows the risk of COVID-19 for mRNA-1273 group with reference to BNT162b2 booster group.

The results for each age category were estimated by Cox regression, adjusted for age, sex, and number of days from the second dose to the start of the sixth wave of COVID-19. Hazard ratios from the age categories were integrated using the random-effects meta-analysis method. Abbreviation: CI, confidence interval; COVID-19, coronavirus disease.

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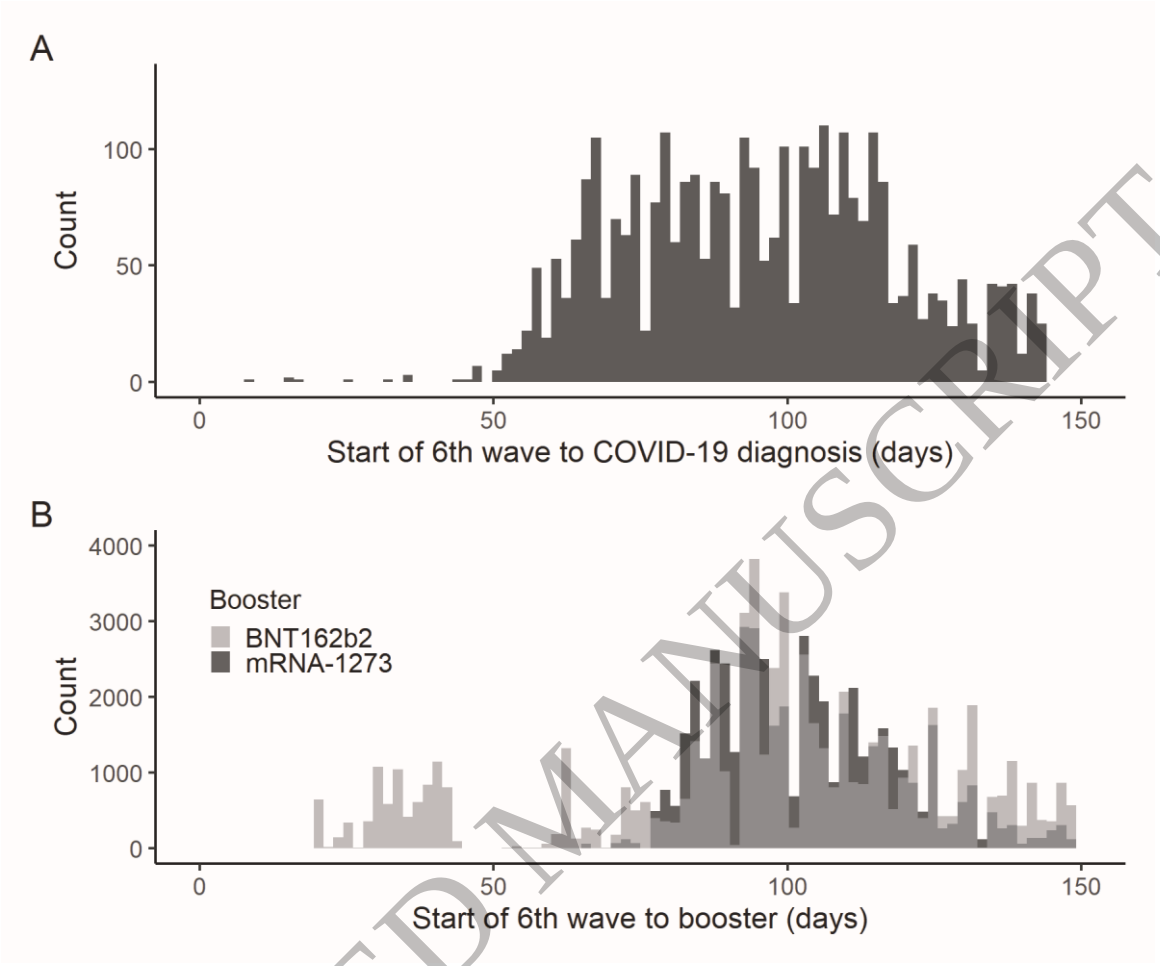

Figure 1

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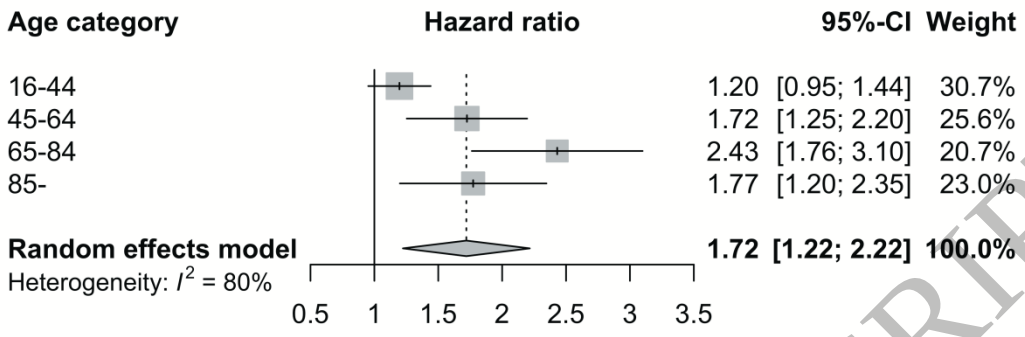
A



B

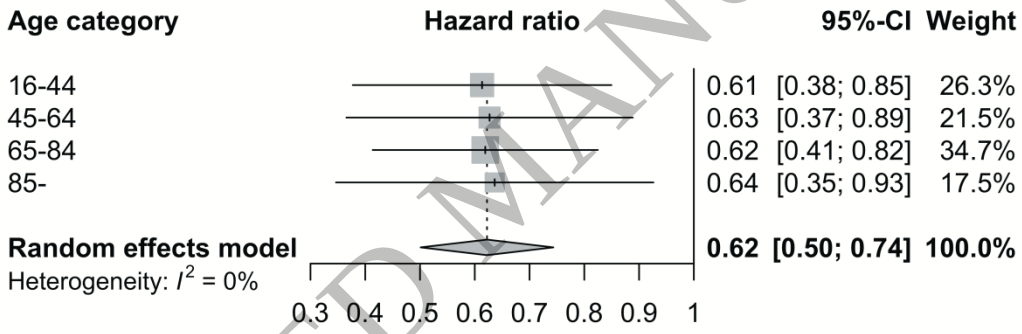


Figure 2

356x356 mm (x DPI)

ACCEPTED MANUSCRIPT