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# Effectiveness of homologous and heterologous BNT162b2 and CoronaVac booster vaccination against severe COVID-19 outcomes

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## Abstract

Introduction: Evidence of the waning immunity of coronavirus disease 2019 (COVID-19) primary vaccination, and immune evasion by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants has led to the rollout of booster vaccination in many countries. Assessing the effectiveness of booster vaccination against severe COVID-19 outcomes is crucial during the transition to endemicity.

Methodology: We conducted a population-based, matched case-control study in Malaysia to estimate the marginal vaccine effectiveness (mVE) of homologous and heterologous BNT162b2 and CoronaVac booster vaccination against COVID-19 related intensive care unit (ICU) admission and death in Delta-predominant and Omicron-predominant periods.

Results: Receipt of a booster vaccination – either homologous or heterologous for CoronaVac, and homologous for BNT162b2 – demonstrated mVE estimates of at least 70% against ICU admission and at least 80% against death, compared to BNT162b2 primary vaccination, in both periods. Overall, the mVE estimates were 10–20 percentage points lower in the Omicron-predominant period than in the Delta-predominant period.

Conclusions: Our study reaffirms that the administration of booster vaccination increases protection against severe COVID-19 outcomes for BNT162b2 and CoronaVac primary vaccination recipients.

**Key words:** SARS-CoV-2; COVID-19; vaccines; BNT162b2; CoronaVac; booster.

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## Introduction

Despite demonstrating substantial initial effectiveness against coronavirus disease 2019 (COVID-19) outcomes, there is global evidence of a significant waning in the protection provided by the primary series of COVID-19 vaccines [1,2]. This prompted the rollout of COVID-19 booster vaccination in many countries. However, as the immune-evasive Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3,4] became globally prevalent in a highly vaccinated world, the continuation of first-generation vaccines as an effective pandemic control measure relied on the prevention of severe disease.

In Malaysia, the BNT162b2 (Pfizer-BioNTech, Puurs, Belgium) and CoronaVac (Sinovac Life Sciences, Beijing, China) vaccines were widely used as primary vaccination under the National COVID-19 Immunization Program (PICK) [5]. Booster vaccination rollout began on October 13, 2021, with BNT162b2 boosters being initially recommended for both BNT162b2 and CoronaVac primary series recipients. Subsequently, CoronaVac boosters were approved on November 17, 2021. As of March 31, 2022, 56.7% of Malaysia's adult population had received a booster dose [6].

In previous studies conducted after the introduction of primary vaccination, we have shown that the receipt of primary vaccination – for both vaccines, BNT162b2 and CoronaVac – was highly effective in preventing COVID-19 related outcomes (infection, symptomatic COVID-19, intensive care unit (ICU) admission, and deaths) [5]. However, the effectiveness of the primary vaccination (for both vaccines) against SARS-CoV-2 infections decreased after 3–5 months [7]. While the effectiveness of BNT162b2 against ICU admission and death was retained, the effectiveness of CoronaVac against ICU admission also decreased after 3–5 months (CoronaVac's effectiveness against death remained stable) [7]. These findings supported the eventual booster vaccination rollout under PICK.

We subsequently observed that the marginal effectiveness of different booster combinations against SARS-CoV-2 infection was 40–50 percentage points lower in the Omicron period (compared to the Delta period), with heterologous booster regimes showing higher effectiveness estimates [8]. Further investigation, however, is required to determine whether the same effectiveness and protection also apply to severe COVID-19 outcomes. Therefore, we conducted a population-based, case-control study in Malaysia to estimate the marginal vaccine effectiveness (mVE) of homologous and heterologous BNT162b2 and CoronaVac booster vaccination against COVID-19 related ICU admission and death in Delta and Omicron predominant periods.

## Methodology

All individuals aged 18 years and older, without a previously documented SARS-CoV-2 infection, and who received BNT162b2 or CoronaVac primary vaccination between July 1, 2021, and September 30, 2021, were included in the analysis. The boosted groups (homologous BNT162b2 ×3 doses, PPP; heterologous CoronaVac ×2 doses + BNT162b2 booster, SSP; homologous CoronaVac ×3 doses, SSS) received their booster dose between November 1, 2021, and February 4, 2022 (Supplementary Figure S1). Individuals were considered "primary vaccinated" and "boosted" at 14 days after the second or third dose, respectively. The overall observation period for outcomes in this study was from November 1, 2021, to March 31, 2022; and February 5, 2022, was determined to be the start of the Omicron-predominant period. This translated to time periods of November 1, 2021, to February 4, 2022, being Delta predominant, and February 5, 2022, to March 31, 2022, being Omicron predominant, for this study. The determination of the starting date for Omicron pre-dominance utilized the Bai-Perron sequential structural break test, as described previously [8], given the absence of a nationally representative genomic surveillance.

Data sources and definitions of outcome measures were previously described [5,7,8]. Cases referred to ICU admissions and deaths. ICU admissions for confirmed cases were based on clinical assessment of whether intensive care was required, and deaths referred to any death attributable to COVID-19. We identified exact matches of each case of ICU admission and death to 10 controls according to the age category (5-year bands), gender, and the presence of comorbidities. mVEs were calculated from the adjusted odds ratios (AOR) estimated from multiple logistic regression using mVE = 100*(1–AOR) with ethnicity, states of residence, and calendar month of the (receipt of) second dose of vaccination used as covariates for adjustment in the regression. Further details on the matching procedure and a flow chart describing the process of selection of samples for this study are provided in Supplementary File S1 and Supplementary Figure 1. All analyses were executed in R 4.1.2 [9], and a significance level of 5% was used for statistical inference.

## Results

The mVE estimates for homologous and heterologous booster vaccination combinations (PPP, SSP, SSS) and CoronaVac primary vaccination (CoronaVac ×2 doses, SS) compared to BNT162b2 primary vaccination (BNT162b2 ×2 doses, PP) are summarized in Table 1. During both the Delta and Omicron predominant periods, receipt of CoronaVac primary vaccination alone (SS, without booster) was

**Table 1.** Marginal vaccine effectiveness (mVE) against ICU admission and death relative to BNT162b2 primary vaccination.

| Outcome | Predominant-Delta (Nov 1, 2021 – Feb 4, 2022) | | | | | Predominant-Omicron (Feb 5, 2022 – Mar 31, 2022) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Vaccination combination | No. of cases | No. of controls | Adj. odds ratio | Adj. mVE (%) | No. of cases | No. of controls | Adj. odds ratio | Adj. mVE (%) |
| ICU Admission | Total | 1485 | 14850 | | | 1165 | 11650 | | |
| | PP | 385 | 2211 | Reference | Reference | 379 | 1298 | Reference | Reference |
| | SS | 919 | 1172 | 5.75 | -475.25 (-581.64, -386.64) | 284 | 951 | 1.34 | -34.39 (-65.66, -9.63) |
| | PPP | 31 | 5285 | 0.02 | 98.13 (97.25, 98.77) | 218 | 4366 | 0.20 | 79.78 (75.17, 83.59) |
| | SSP | 128 | 4986 | 0.10 | 90.42 (87.70, 92.58) | 244 | 4113 | 0.28 | 72.23 (66.26, 77.17) |
| | SSS | 22 | 1196 | 0.07 | 93.15 (89.29, 95.81) | 40 | 922 | 0.29 | 70.62 (57.72, 80.03) |
| Death | Total | 1018 | 10180 | | | 1320 | 13200 | | |
| | PP | 302 | 1364 | Reference | Reference | 464 | 1770 | Reference | Reference |
| | SS | 643 | 903 | 4.69 | -368.94 (-466.74, -289.16) | 370 | 1062 | 1.48 | -47.96 (-76.03,-24.31) |
| | PPP | 10 | 3712 | 0.01 | 99.28 (98.70, 99.65) | 207 | 4670 | 0.15 | 84.87 (81.44, 87.71) |
| | SSP | 56 | 3530 | 0.05 | 95.32 (93.60, 96.62) | 232 | 4442 | 0.19 | 80.72 (76.68, 84.09) |
| | SSS | 7 | 671 | 0.02 | 97.52 (94.94, 98.97) | 47 | 1256 | 0.17 | 82.81 (75.82, 88.00) |

Adj.: Adjusted; PPP: 3x BNT162b2; SSP: 2x CoronaVac + BNT162b2; SSS: 3x CoronaVac; SS: 2x CoronaVac; PP: 2x BNT162b2 (reference group); ICU: intensive care unit.

associated with higher odds for ICU admission and death when compared to BNT162b2 primary vaccination (PP). However, subsequent receipt of a homologous (SSS) or heterologous (SSP) booster dose significantly reduced the odds, with estimated mVEs of at least 70% against ICU admission and at least 80% against death compared to PP. The mVEs of SSS and SSP were slightly lower than PPP in the Delta-predominant period but were comparable in the Omicron-predominant period. In general, mVEs against ICU admission and death were lower by an estimated 10–20 percentage points in the Omicron period than in the Delta period, across boosted groups. Baseline characteristics for cases and controls for both analyses are provided in Supplementary Table 1 for ICU admissions and Supplementary Table 2 for COVID-19 deaths. A graphical representation of the mVEs described above is also provided in Supplementary Figure 2.

## Discussion

The CoronaVac primary series recipients showed substantial waning of the effect of the vaccine after 3–5 months [7]. Our study showed that receipt of a booster dose, either homologous (SSS) or heterologous (SSP), provided at least 70–80% mVE against ICU admission and death during the Omicron-predominant period, compared to the BNT162b2 primary series. SSS and SSP were also found to be highly effective against severe COVID-19 outcomes in other countries [10,11]. In Chile, both homologous and heterologous booster vaccinations have been reported to provide high levels of protection against COVID-19, including against severe disease and death, in CoronaVac primary vaccination recipients [10]. Another study conducted in Brazil also observed high levels of effectiveness against severe outcomes in both Delta and Omicron predominance periods for those who received CoronaVac and BNT162b2 booster vaccinations [11].

Similarly, our findings of high mVE estimates for homologous booster vaccination (PPP) in BNT162b2 primary series recipients are consistent with evidence from other settings [12,13]. Although mVE estimates were lower during the Omicron-predominant period, PPP still demonstrated an estimated 80–85% mVE against ICU admission and death compared to PP. This was similar to the relative VE of 88% against ICU admission or death observed in a previous study, which was also conducted during the Omicron-predominant period, when a third dose of BNT162b2 was compared to the BNT162b2 primary series [12]. Another study in the United States reported 78.8% effectiveness against death when comparing these two groups after the emergence of the Omicron variant [13].

Overall, our study findings support the existing evidence that booster vaccinations are effective and increase protection against severe COVID-19 outcomes for recipients of the BNT162b2 and CoronaVac primary vaccinations. Our study draws strength from the investigation of mVE estimates for both homologous and heterologous boosting regimes for CoronaVac primary recipients in a low-to-middle-income country (LMIC), where CoronaVac vaccines were widely utilized. However, in this study, we were limited by the short follow-up period and the lack of detailed and nationally representative genomic surveillance, which rendered us unable to further investigate the possible waning of booster vaccination effectiveness over time and possible differences in vaccination effectiveness against specific Omicron variant lineages. We were also unable to rule out (and, if present, quantify) the presence of other circulating SARS-CoV-2 variants during the Delta and Omicron predominance periods analyzed in this study. Finally, we were unable to report mVE estimates for other COVID-19 vaccines used in Malaysia due to the limited number of severe outcomes observed as vaccines other than BNT162b2 and CoronaVac were not widely utilized during the primary vaccination rollout under PICK.

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### Ethical consideration

This study is part of 'The Real-World Evaluation of COVID-19 Vaccines' under the Malaysia National COVID-19 Immunization Program (RECoVaM) study registered in the National Medical Research Register (NMRR-21-1660-60697). This study was granted ethical approval by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia.

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## Conflict of interests

JLS received support from AstraZeneca for attending academic meetings for work outside this paper. All other authors declare no conflict of interests.

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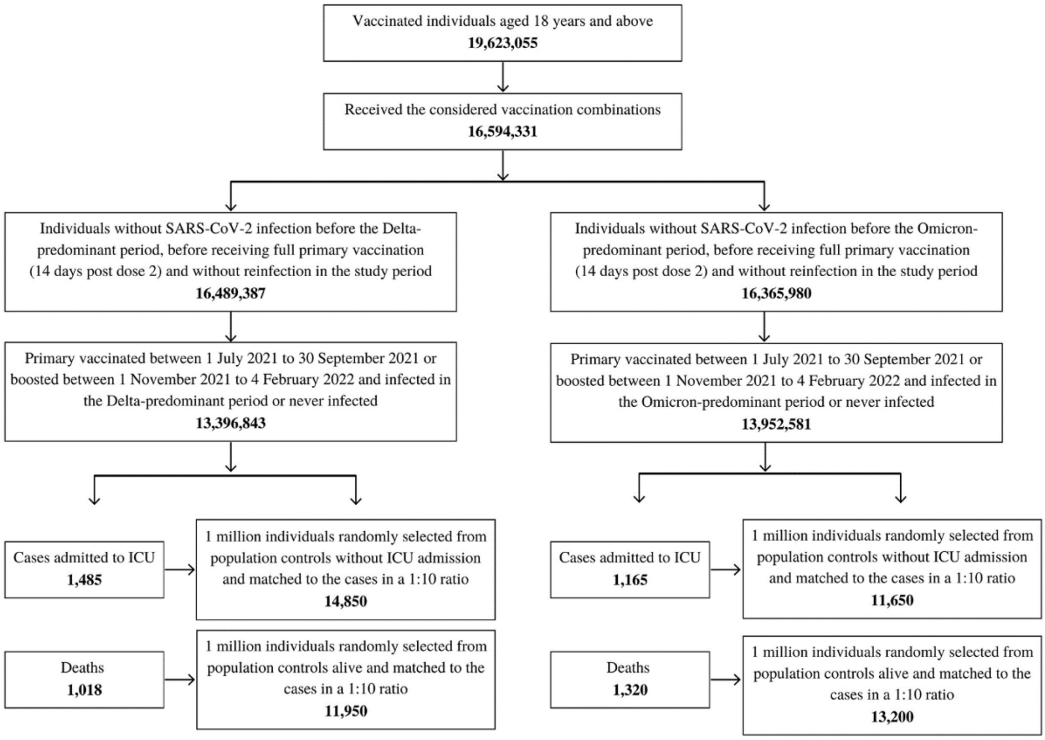
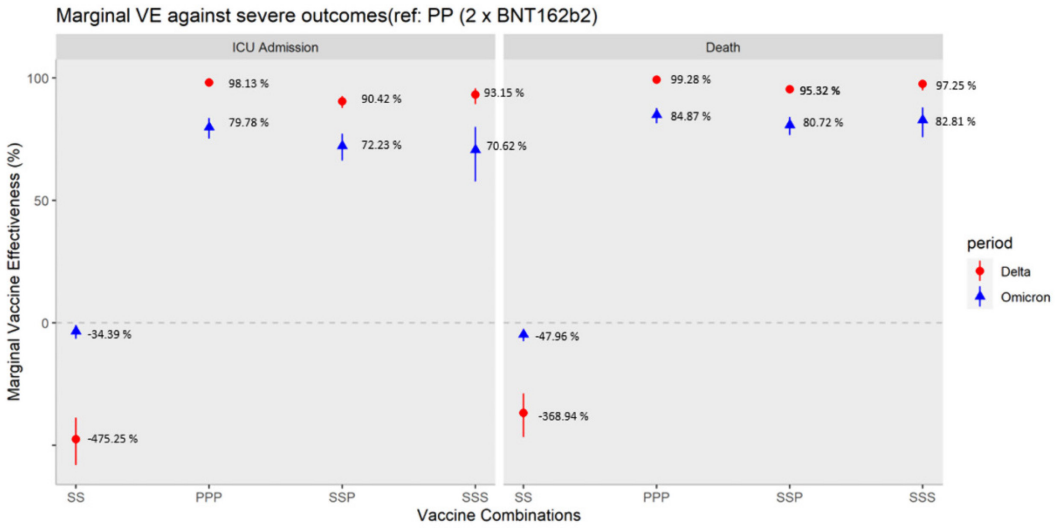
## Annex – Supplementary materials

**Supplementary Figure 1.** Flow chart of study samples selection (matched case–control design).




ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Supplementary Figure 2.** Adjusted marginal vaccine effectiveness (VE) estimates against intensive care unit (ICU) admission and death relative to BNT162b2 primary vaccination (Delta and Omicron predominant periods).




PPP, ×3 BNT162b2; SSP, ×2 CoronaVac + BNT162b2; SSS, ×3 CoronaVac; SS, ×2 CoronaVac; PP, ×2 BNT162b2 (reference group).

**Supplementary File 1.** Methods and study samples selection.

## Methods: case control matching procedure

Severe coronavirus disease 2019 (COVID-19) outcomes of interest in this study included COVID-19 related intensive care unit (ICU) admission and death. Every 1 case of ICU admission and death was matched to 10 controls, with replacement dataset derived by using the ccoptimalmatch R package (R.4.1.2) following multiple steps; which included matching on exact variables, followed by building artificial observations for controls allowing optimal matching, and then ordering of controls to allow for the closest controls to be matched to the case, and a final algorithm that generated a matched dataset by the specified ratio (10 controls: 1 case). The variables used for matching in this study were age (in 5-year bands), gender, and the presence of comorbidities (yes or none).

## Study samples selection for cases and controls

The flow of study samples selection of cases and controls is depicted in Supplementary Figure S1. There were 1,486 and 1,018 ICU admissions in the Delta and Omicron predominant periods, respectively. There were 1,165 and 1,320 deaths during the Delta and Omicron pre-dominant periods. Every 1 case of ICU admission and death in both periods was matched to 10 controls (procedure described above).

The eligible population for controls selection included all vaccinated individuals aged ≥ 18 years, living in Malaysia, and without the outcomes (ICU admission and death). In this study, only those who received either BNT162b2 or CoronaVac primary vaccination were analyzed, and accordingly, other vaccine combinations were excluded from further analysis. Individuals with documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection(s) prior to or after the specified study observation periods for Delta (November 1, 2021, to February 4, 2022) and Omicron (February 5, 2022, to March 31,2022) predominance were excluded. All other vaccinated individuals were eligible for selection as controls, regardless of their SARS-CoV-2 infection status during the respective study observation periods. One million individuals were randomly selected from the remaining eligible individuals (total > 13 million individuals), before they were matched to the cases according to the specified ratio (10 controls: 1 case).

**Supplementary Table 1.** Baseline characteristics for individuals admitted to the intensive care unit (ICU) in the Delta predominant period (November 1, 2021, to February 4, 2022) and the Omicron predominant period (February 5, 2022, to March 31, 2022), and their matched controls.

| Vaccine combinations | Cases (ICU admission) | | | | | Controls | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ×2 BNT162b2 | ×2 CoronaVac | ×3 BNT162b2 | ×2 CoronaVac +BNT162b2B | ×3 CoronaVac | ×2 BNT162b2 | ×2 CoronaVac | ×3 BNT162b2 | ×2 CoronaVac +BNT162b2B | ×3 CoronaVac |
| **Delta predominant** | | | | | | | | | | |
| **Total No. of individuals** | | | **N = 1485** | | | | | **N = 14850** | | |
| No. of individuals per treatment | n = 385 | n = 919 | n = 31 | n = 128 | n = 22 | n = 2211 | n = 1172 | n = 5285 | n = 4986 | n = 1196 |
| Gender: male | 212 (55.1) | 489 (53.2) | 25 (80.6) | 91 (71.1) | 14 (63.6) | 1463 (66.2) | 521 (44.5) | 2531 (47.9) | 3117 (62.5) | 678 (56.7) |
| Presence of comorbidity: yes | 349 (90.6) | 753 (81.9) | 27 (87.1) | 103 (80.5) | 17 (77.3) | 1794 (81.1) | 1022 (87.2) | 4527 (85.7) | 4126 (82.8) | 1021 (85.4) |
| **Age (years)** | | | | | | | | | | |
| 18–39 | 32 (8.3) | 85 (9.2) | 2 (6.5) | 13 (10.2) | 0 (0.0) | 229 (10.4) | 219 (18.7) | 281 (5.3) | 439 (8.8) | 121 (10.1) |
| 40–59 | 158 (41.0) | 334 (36.3) | 16 (51.6) | 43 (33.6) | 8 (36.4) | 649 (29.4) | 333 (28.4) | 2146 (40.6) | 1787 (35.8) | 382 (31.9) |
| > 60 | 195 (50.6) | 500 (54.4) | 13 (41.9) | 72 (56.2) | 14 (63.6) | 1333 (60.3) | 620 (52.9) | 2858 (54.1) | 2760 (55.4) | 693 (57.9) |
| **Time since second dose** | | | | | | | | | | |
| 0–3 months | 220 (57.1) | 567 (61.7) | 5 (16.1) | 52 (40.6) | 7 (31.8) | 1272 (57.5) | 967 (82.5) | 2082 (39.4) | 2300 (46.1) | 638 (53.3) |
| 3–6 months | 165 (42.9) | 352 (38.3) | 23 (74.2) | 76 (59.4) | 15 (68.2) | 939 (42.5) | 205 (17.5) | 3086 (58.4) | 2686 (53.9) | 558 (46.7) |
| > 6 months | 0 (0.0) | 0 (0.0) | 3 (9.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 117 (2.2) | 0 (0.0) | 0 (0.0) |
| **Omicron predominant** | | | | | | | | | | |
| **Total No. of individuals** | | | **N = 1165** | | | | | **N = 11650** | | |
| No. of individuals per treatment | n = 379 | n = 284 | n = 218 | n = 244 | n = 40 | n = 1298 | n = 951 | n = 4366 | n = 4113 | n = 922 |
| Gender: male | 221 (58.3) | 159 (56.0) | 131 (60.1) | 162 (66.4) | 26 (65.0) | 719 (55.4) | 536 (56.4) | 2853 (65.3) | 2271 (55.2) | 611 (66.3) |
| Presence of comorbidity: yes | 325 (85.8) | 223 (78.5) | 187 (85.8) | 198 (81.1) | 31 (77.5) | 1067 (82.2) | 760 (79.9) | 3721 (85.2) | 3347 (81.4) | 745 (80.8) |
| **Age (years)** | | | | | | | | | | |
| 18–39 | 54 (14.2) | 40 (14.1) | 23 (10.6) | 36 (14.8) | 3 (7.5) | 227 (17.5) | 166 (17.5) | 442 (10.1) | 545 (13.3) | 98 (10.6) |
| 40–59 | 129 (34.0) | 85 (29.9) | 73 (33.5) | 78 (32.0) | 9 (22.5) | 490 (37.8) | 187 (19.7) | 1358 (31.1) | 1531 (37.2) | 260 (28.2) |
| > 60 | 196 (51.7) | 159 (56.0) | 122 (56.0) | 130 (53.3) | 28 (70.0) | 581 (44.8) | 598 (62.9) | 2566 (58.8) | 2037 (49.5) | 564 (61.2) |
| **Time since second dose** | | | | | | | | | | |
| 3–6 months | 252 (66.5) | 200 (70.4) | 59 (27.1) | 128 (52.5) | 21 (52.5) | 852 (65.6) | 683 (71.8) | 2060 (47.2) | 2259 (54.9) | 448 (48.6) |
| > 6 months | 127 (33.5) | 84 (29.6) | 159 (72.9) | 116 (47.5) | 19 (47.5) | 446 (34.4) | 268 (28.2) | 2306 (52.8) | 1854 (45.1) | 474 (51.4) |

Controls were matched for age in 5-year bands, gender, and the presence of comorbidities.

**Supplementary Table 2.** Baseline characteristics of coronavirus disease 2019 (COVID-19) deaths in the Delta predominant period (November 1, 2021, to February 4, 2022) and the Omicron predominant period (February 5, 2022, to March 31, 2022), and their matched controls.

| Vaccine combinations | Cases (Deaths) | | | | | Controls | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ×2 BNT162b2 | ×2 CoronaVac | ×3 BNT162b2 | ×2 CoronaVac +BNT162b2B | ×3 CoronaVac | ×2 BNT162b2 | ×2 CoronaVac | ×3 BNT162b2 | ×2 CoronaVac +BNT162b2B | ×3 CoronaVac |
| **Delta predominant Total No. of Individuals** | | | **N = 1018** | | | | | **N = 10180** | | |
| No. of individuals per treatment | n = 302 | n = 643 | n = 10 | n = 56 | n = 7 | n = 1364 | n = 903 | n = 3712 | n = 3530 | n = 671 |
| Gender: male | 187 (61.9) | 389 (60.5) | 7 (70.0) | 39 (69.6) | 5 (71.4) | 886 (65.0) | 668 (74.0) | 2222 (59.9) | 2094 (59.3) | 400 (59.6) |
| Presence of comorbidity: Yes | 279 (92.4) | 543 (84.4) | 10 (100.0) | 46 (82.1) | 4 (57.1) | 1166 (85.5) | 754 (83.5) | 3301 (88.9) | 3081 (87.3) | 518 (77.2) |
| **Age (years)** | | | | | | | | | | |
| 18–39 | 8 (2.6) | 36 (5.6) | 0 (0.0) | 1 (1.8) | 0 (0.0) | 93 (6.8) | 55 (6.1) | 127 (3.4) | 194 (5.5) | 11 (1.6) |
| 40–59 | 72 (23.8) | 154 (24.0) | 1 (10.0) | 12 (21.4) | 2 (28.6) | 343 (25.1) | 240 (26.6) | 878 (23.7) | 746 (21.1) | 217 (32.3) |
| > 60 | 222 (73.5) | 453 (70.5) | 9 (90.0) | 43 (76.8) | 5 (71.4) | 928 (68.0) | 608 (67.3) | 2707 (72.9) | 2590 (73.4) | 443 (66.0) |
| **Time since second dose** | | | | | | | | | | |
| 0–3 months | 162 (53.6) | 374 (58.2) | 3 (30.0) | 22 (39.3) | 3 (42.9) | 895 (65.6) | 425 (47.1) | 1025 (27.6) | 1284 (36.4) | 175 (26.1) |
| 3–6 months | 140 (46.4) | 269 (41.8) | 7 (70.0) | 34 (60.7) | 4 (57.1) | 469 (34.4) | 478 (52.9) | 2646 (71.3) | 2246 (63.6) | 496 (73.9) |
| > 6 months | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 41 (1.1) | 0 (0.0) | 0 (0.0) |
| **Omicron predominant Total No. of Individuals** | | | **N = 1320** | | | | | **N = 13200** | | |
| No. individuals per treatment | n = 464 | n = 370 | n = 207 | n = 232 | n = 47 | n = 1770 | n = 1062 | n = 4670 | n = 4442 | n = 1256 |
| Gender: male | 267 (57.5) | 202 (54.6) | 141 (68.1) | 154 (66.4) | 22 (46.8) | 1256 (71.0) | 625 (58.9) | 2589 (55.4) | 2677 (60.3) | 713 (56.8) |
| Presence of comorbidity: yes | 412 (88.8) | 293 (79.2) | 184 (88.9) | 188 (81.0) | 37 (78.7) | 1487 (84.0) | 825 (77.7) | 4022 (86.1) | 3745 (84.3) | 1061 (84.5) |
| **Age (years)** | | | | | | | | | | |
| 18–39 | 23 (5.0) | 13 (3.5) | 9 (4.3) | 9 (3.9) | 4 (8.5) | 136 (7.7) | 48 (4.5) | 189 (4.0) | 162 (3.6) | 28 (2.2) |
| 40–59 | 110 (23.7) | 75 (20.3) | 42 (20.3) | 57 (24.6) | 8 (17.0) | 313 (17.7) | 274 (25.8) | 942 (20.2) | 1097 (24.7) | 137 (10.9) |
| > 60 | 331 (71.3) | 282 (76.2) | 156 (75.4) | 166 (71.6) | 35 (74.5) | 1321 (74.6) | 740 (69.7) | 3539 (75.8) | 3183 (71.7) | 1091 (86.9) |
| **Time since second dose** | | | | | | | | | | |
| 3–6 months | 296 (63.8) | 261 (70.5) | 71 (34.3) | 111 (47.8) | 28 (59.6) | 1241 (70.1) | 705 (66.4) | 1864 (39.9) | 1953 (44.0) | 789 (62.8) |
| > 6 months | 168 (36.2) | 109 (29.5) | 136 (65.7) | 121 (52.2) | 19 (40.4) | 529 (29.9) | 357 (33.6) | 2806 (60.1) | 2489 (56.0) | 467 (37.2) |

Controls were matched for age in 5-year bands, gender, and the presence of comorbidities.