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# Incidence rates of myocarditis and pericarditis within 30 days following homologous and heterologous BNT162b2 vaccinations in individuals 5–40 years of age

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ABSTRACT

*Introduction:* Due to the data scarcity in low- and middle-income countries, we aimed to examine the incidence rate of myocarditis and pericarditis within 30 days after each dose of homologous (3 × BNT162b2) and heterologous prime-boost (2 × BBIBP-CorV/BNT162b2) vaccine regimen among individuals younger than 40 years.
*Methods:* We conducted a historical control cohort using routinely recorded data from Thai national vaccine and insurance claims databases. Sex-specific incidence rate ratios (IRRs) for myocarditis and pericarditis were calculated for each vaccination strategy and contrasted with incidence rates among the non-immunised population in the pre-COVID-19 period. From August 2021 to September 2022, we tracked the incidence of myocarditis and pericarditis within 30 days after vaccinations using < 40-year-old national population databases. Our reference was the average monthly incidence of these conditions in the non-immunised population from August to October 2019. The exposure of interest was immunisation against the SARS-CoV-2 virus, incorporating the following vaccination strategies: three-dose 3 × BNT162b2 regimen, three-dose 2 × BBIBP-CorV/BNT162b2 regimen, and non-immunisation.
*Results:* For myocarditis, a total of 215 cases were identified among 7,594,965 individuals in the 3 × BNT162b2 cohort, 5 cases among 2,914,643 individuals in the 2 × BBIBP-CorV/BNT162b2 cohort, and 115 cases among 32,424,780 non-immunised individuals. The sex-specific IRRs (95 % confidence intervals) of myocarditis and pericarditis after the homologous vaccination were 3.09 (1.61, 5.93) and 1.84 (0.72, 4.73) for females and 7.43 (3.11, 17.73) and 10.48 (3.90, 28.15) for males, respectively. Conversely, the IRRs of myocarditis after the heterologous vaccination were not significant (females: 2.24 (0.70, 7.17); males: 1.99 (0.48, 8.21)). IRRs could not be obtained for pericarditis after the heterologous vaccination because of the small number of observed events.
*Conclusions:* The study observed a significantly increased risk of myocarditis and pericarditis following homologous 3 × BNT162b2 vaccination but had insufficient power to confirm an increased risk for myocarditis following the heterologous prime-boost 2 × BBIBP-CorV/BNT162b2 vaccination. The incidence of pericarditis following the heterologous vaccination was too rare to evaluate.

## 1. Introduction

As of June 2023, over 13 billion doses of coronavirus disease (COVID-19) vaccine have been administered worldwide [1]. Messenger ribonucleic acid (mRNA) vaccines, specifically BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), received emergency use authorisation [2,3] and have been widely accepted globally owing to their efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [4,5]. Numerous large-scale studies observed increases in myocarditis and pericarditis cases following vaccination

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with mRNA vaccines, but these did not include children under 12 years of age [6–10]. These events occur mostly in younger populations, specifically male adolescents [6–10]. Most events occur after the second dose of vaccine, and the incidence decreases slightly after the third dose [7,9,11,12].

Importantly, these studies have predominantly been confined to homologous [6–12] or heterologous [13] mRNA vaccine schedules, thus potentially limiting their generalizability to low- and middle-income countries, where the use of heterologous prime-boost immunisation with inactivated virus and mRNA vaccines is higher than that in high-income countries [14].

Given the diversity of vaccine types, and different vaccines becoming available at different times, most vaccinations in Thailand have been heterologous prime-boost combinations [15]. The national vaccination campaign was initiated on 28 February 2021, and used the CoronaVac (Sinovac) vaccine in individuals aged between 18 and 60 years and the ChAdOx1 (AstraZeneca) vaccine in those older than 60 years. Healthcare workers and individuals with chronic comorbidities were prioritised during the initial stage. Subsequently, the BBIBP-CorV (Sinopharm) vaccine was imported and approved for administration in Thailand on 20 June 2021. Administration of the BNT162b2 vaccine started on 26 August 2021. BBIBP-CorV and BNT162b2 vaccines were mainly administered to children and adolescents aged 5–18 years. Consequently, two primary vaccine regimens were established for the BNT162b2 vaccine, catering primarily to individuals younger than 40 years of age: homologous three-dose 3 × BNT162b2 and heterologous three-dose 2 × BBIBP-CorV/BNT162b2 vaccine series [16].

Since 2015, the National Health Security Office (NHSO) in Thailand has mandated all public and private hospitals to submit summaries of their inpatient records, irrespective of health insurance status. The NHSO, leveraging unique citizen identification numbers, can link inpatient data with corresponding vaccinations, COVID-19 claims, and vital registry databases. By using the International Classification of Diseases, 10th revision (ICD-10) codes, it is possible to link hospitalisations related to myocarditis (ICD-10 codes: I40.x, I41.x, and I51.4) and pericarditis (ICD-10 codes: I30.x and I32.x) with preceding vaccination events. Hence, we were able to use the combined data to conduct a population-based cohort study, which provides stronger evidence regarding causality than the case-control study that was conducted by the Department of Disease Control [17].

Therefore, this study aimed to examine the incidence rate of myocarditis and pericarditis within 30 days after both homologous 3 × BNT162b2 vaccination and heterologous prime-boost 2 × BBIBP-CorV/BNT162b2 vaccination in individuals aged 5–40 years. To do this, we used the incidence rates observed in the non-immunised population during the pre-COVID-19 period as the reference, and the unvaccinated SARS-CoV-2 test-positive population as the SARS-CoV-2-infected group (additional comparative group: first immunisation by natural infection).

## 2. Methods

### 2.1. Ethics statements

The Human Research Ethics Committee of Prince of Songkla University approved this study (approval number: REC 65–460-18–1). According to the Thai Personal Data Protection Act 2019, Thailand, patient data were de-identified to ensure anonymisation of personal data. Because the data were de-identified, informed consent was not required.

### 2.2. Data sources

Due to the COVID-19 pandemic, all data related to reverse transcription polymerase chain reaction (RT-PCR) testing, vaccination, and hospitalisation were solely managed by the government under the COVID-19 Emergency Decree between May and October 2021, with financial support from the NHSO [18]. In the Thai contact-tracing system, all individuals with a history of contact with a patient infected with SARS-CoV-2 were required undergo testing using both an antigen test kit (ATK) and RT-PCR [19].

Under the national guidelines, individuals presenting with acute symptoms, including chest pain, dyspnoea, palpitation, or syncope, were hospitalised for potential myocarditis and pericarditis [20]. These diagnoses were subsequently documented in the NHSO claims database. All such records were registered in accordance with the Emergency Decree management system. All data were linked to the NHSO database, and our research team was granted access to analyse the data. As permitted, we had access to the encrypted national databases from August 2018 to September 2022.

We integrated data from the NHSO, including records of COVID-19 vaccinations, inpatient claims, RT-PCR results confirming SARS-CoV-2 infection, and the vital registry. These data were linked using encrypted citizen identification numbers. However, after December 2021, the Omicron variant caused a surge in infections, overwhelming the health system. Consequently, the national policy shifted to encourage testing using ATKs without confirmation using RT-PCR [21]. Hence, for each vaccination group, we included the vaccination records of individuals who had no record of a positive ATK or RT-PCR test. Additionally, we limited our data to patients whose first SARS-CoV-2 infection, confirmed by RT-PCR, occurred before December 2021.

### 2.3. Study design

This historical control cohort study used national databases encompassing data from the entire population to form non-concurrent cohorts, recognising that individuals from each cohort were not mutually exclusive. The reference cohort consisted of non-immunised individuals during the pre-COVID-19 period. This cohort was subsequently compared with two vaccination cohorts (homologous 3 × BNT162b2 vaccination and heterologous prime-boost vaccination with 2 × BBIBP-CorV/BNT162b2) and the first SARS-CoV-2 infection cohort during Delta variant-dominant period, as shown in Fig. 1 [22].

### 2.4. Participant recruitment

Individuals were categorised into three age groups: 5–11, 12–17, and 18–40 years. The implementation of vaccination corresponded to these age groups, starting with 18–40 years, followed by 12–17 years, and then 5–11 years [16]. For each group, we aimed to follow up each individual for 30 days as a person-month. Those with no previous COVID-19 registration were recruited during the periods shown in Fig. 1, as this offered the greatest amount of person-month follow-up time within a span of 3 months for the first SARS-CoV-2 infection (Delta dominance), first and second doses of vaccine, and 6 months for the third dose of vaccine. (The interval between the second and third doses of vaccine varied from 10 to 30 weeks.).

The reference cohort comprised non-immunised individuals aged 5–40 years from August to October 2019 (accessible data from the pre-COVID-19 pandemic period). During the Delta dominant period from August to October 2021, we also included a group of individuals who had SARS-CoV-2 infection (positive RT-PCR test) as their first immunisation.

### 2.5. Outcomes and follow-up

The outcome variables were hospitalisation for myocarditis (ICD-10 codes: I40.x, I41.x, and I51.4) and pericarditis (ICD-10 codes: I30.x and I32.x) recorded within a 30-day interval after each vaccination dose or SARS-CoV-2 infection (since the date of laboratory request). According to the vaccine policy, patients could receive the first dose of the COVID-19 vaccine at least 30 days after the day of the positive test result [16]. Hence, there was a minimum 30-day follow-up period without vaccination for each individual with SARS-CoV-2 infection during the Delta

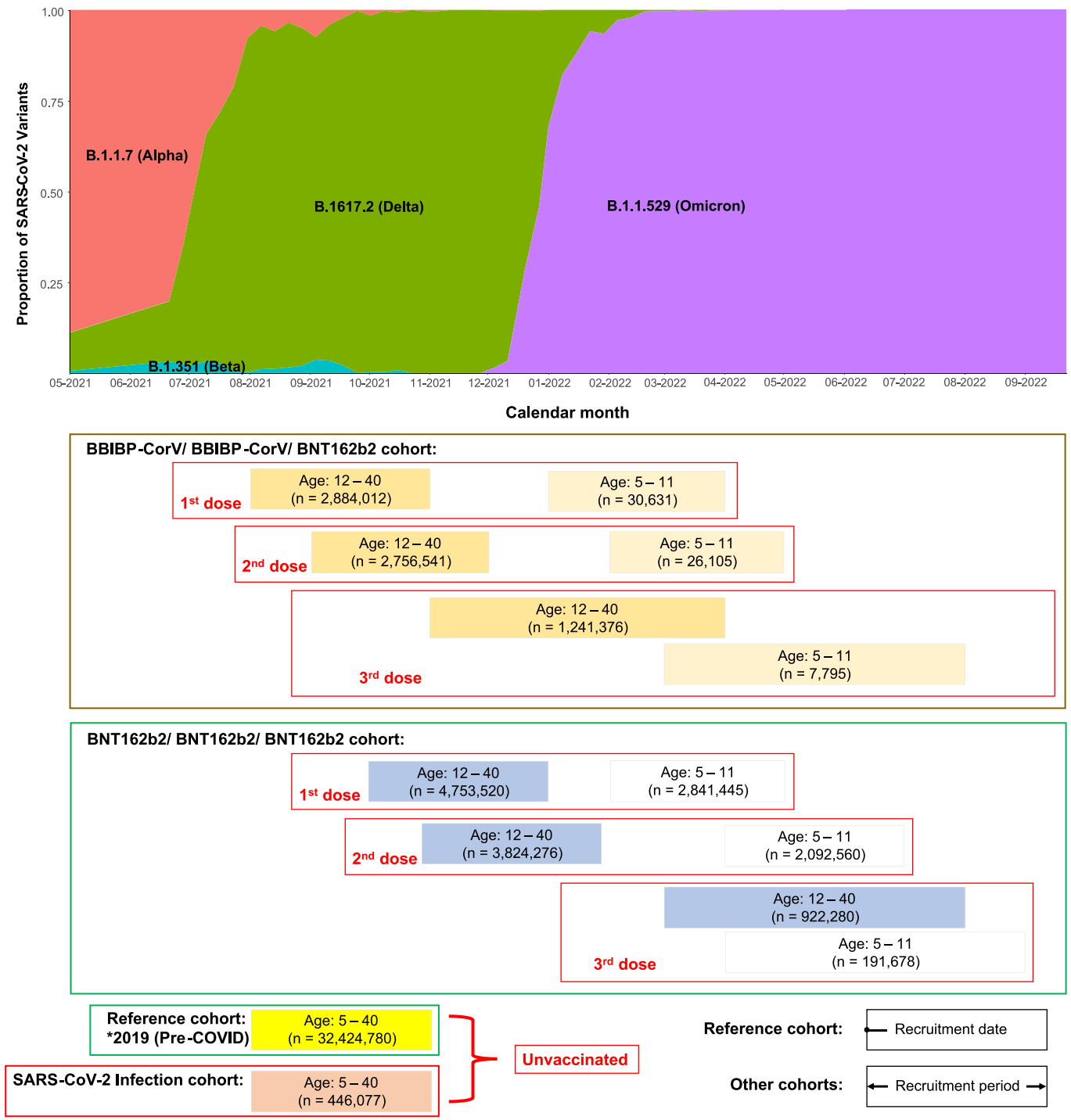


**Fig. 1.** Recruitment of individuals for the comparative cohorts.The time series of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants (top) was generated from surveillance data of the Department of Medical Sciences, Ministry of Public Health.

dominant period.

In the non-immunised population, we did not evaluate individuals as in other cohorts but used the entire non-immunised population to calculate the incidence rate. This method provided a statistical value for the 3-month average incidence rate from August to October 2019. This was then compared with the incidence rates within a month (30 days) of follow-up in the other cohorts.

The time point of censoring included any of three events: testing positive for SARS-CoV-2 (RT-PCR or ATK) after vaccination, receiving another dose of the COVID-19 vaccine before the end of the follow-up period, or death.

### 2.6. Exposure and stratification

The exposure consisted of four principal immunisation statuses: non-immunisation (reference group), first SARS-CoV-2 infection (natural immunisation), homologous three-dose 3 × BNT162b2 vaccination, and heterologous prime-boost vaccination with three-dose 2 × BBIBP-CorV/ BNT162b2. Each vaccination group was further divided into three subgroups corresponding to the first, second, and third doses. The individuals were further stratified according to age group and sex for statistical analysis.

### 2.7. Statistical analysis

Using descriptive statistics, we assembled a summary of the demographic data for the entire population for each immunisation status and individuals hospitalised due to myocarditis and pericarditis. Subsequently, we presented these data visually, depicting the counts of events alongside person-months (30 days) at risk for each age-sex-immunisation subgroup. Additionally, we compiled forest plots of the incidence rate ratios (IRRs) relative to the reference group, including their 95 % confidence intervals. We used the Mantel–Haensel method to calculated pooled IRRs from the results of the various subgroups into sex-specific all-ages-combined IRRs for each dose and overall [23]. The level of statistical heterogeneity among the subgroups was estimated using the $I^2$ statistic [24]. We used a fixed-effects model to account for the pooled effect of the IRRs if there was no significant heterogeneity among the subgroups ($I^2 < 50$ %), and a random-effects model if significant heterogeneity was present [24].

All analyses were performed using the epiDisplay (version 3.5.0.2) [25], meta (version 6.2.1) [26], and tidyverse (version 1.3.1) [27] packages in R language and environment version 4.1.1 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Two-sided P-values $< 0.05$ were considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

A sequential vaccination strategy was adopted, beginning with adults and progressing to adolescents and children, owing to safety considerations. This approach precluded the possibility of concurrent recruitment across all cohorts for comparison. Fig. 1 illustrates the recruitment of individuals during the Delta and Omicron variant-dominant periods from August 2021 to September 2022, the period for which data use was approved. The figure shows the 3/6-month recruitment period for each dose and age-group in the other cohorts. From August to October 2019, the non-immunised cohort (reference group) comprised 32,424,780 individuals.

Table 1 shows that the homologous vaccination cohort (n = 7,594,965) was larger than the heterologous vaccination cohort (n = 2,914,643) at both time points. Female vaccine recipients outnumbered male vaccine recipients in all cohorts. The 18–40-year age group was the largest age group in the heterologous vaccination, SARS-CoV-2 infection, and reference cohorts. Conversely, the 12–17-year age group was the largest age group in the homologous vaccination cohort. The interval between doses was shorter in the heterologous vaccination group than in the homologous vaccination group.

Table 2 provides details of hospitalised patients with myocarditis and

**Table 1**
Comparison of characteristics between individuals recruited who received a COVID-19 vaccination or had first SARS-CoV-2 infection and the non-immunised population (reference group).

| Total number of individuals | **Homologous BNT162b2 vaccination** | | | **Heterologous prime-boost vaccination** | | | **Unvaccinated individuals** | |
|---|---|---|---|---|---|---|---|---|
| | **Sequence = BNT162b2/BNT162b2/BNT162b2** | | | **Sequence = BBIBP-CorV/BBIBP-CorV/BNT162b2** | | | | |
| | **First dose** | **Second dose** | **Third dose** | **First dose** | **Second dose** | **Third dose** | **First SARS-CoV-2 infection during the dominant Delta variant period** | **Non-immunised population(reference group)** |
| | (n = 7,594,965) | (n = 5,916,836) | (n = 1,113,958) | (n = 2,914,643) | (n = 2,782,646) | (n = 1,249,171) | (n = 446,077) | (n = 32,424,780) |
| **Sex** | | | | | | | | |
| Female | 3,817,627 (50.3) | 3,019,569 (51.0) | 666,404 (59.8) | 1,517,809 (52.1) | 1,451,540 (52.2) | 689,122 (55.2) | 226,454 (50.8) | 15,944,806 (49.2) |
| Male | 3,777,338 (49.7) | 2,897,267 (49.0) | 447,554 (40.2) | 1,396,834 (47.9) | 1,331,106 (47.8) | 560,049 (44.8) | 219,623 (49.2) | 16,479,974 (50.8) |
| **Age** | | | | | | | | |
| 5–11 years | 2,841,445 (37.4) | 2,092,560 (35.4) | 191,678 (17.2) | 30,631 (1.1) | 26,105 (0.9) | 7,795 (0.6) | 39,133 (8.8) | 5,569,710 (17.2) |
| 12–17 years | 3,821,510 (50.3) | 3,091,247 (52.2) | 839,206 (75.3) | 82,237 (2.8) | 80,326 (2.9) | 26,960 (2.2) | 60,086 (13.4) | 4,849,696 (15.0) |
| 18–40 years | 932,010 (12.3) | 733,029 (12.4) | 83,074 (7.5) | 2,801,775 (96.1) | 2,676,215 (96.2) | 1,214,416 (97.2) | 346,858 (77.8) | 22,005,374 (67.9) |
| **Interval from the previous vaccine dose [median interval (IQR), days]** | | | | | | | | |
| Overall | – | 27 (21, 56) | 185 (162, 205) | – | 21 (21, 28) | 107 (84, 135) | – | – |
| Females | | | | | | | | |
| 5–11 years | – | 56 (46, 61) | 176 (139, 206) | – | 21 (21, 26) | 111 (83, 149) | – | – |
| 12–17 years | – | 21 (21, 26) | 189 (172, 205) | – | 21 (21, 27) | 102 (80, 137) | – | – |
| 18–40 years | – | 25 (21, 29) | 175 (128, 207) | – | 21 (21, 28) | 105 (81, 132) | – | – |
| Males | | | | | | | | |
| 5–11 years | – | 56 (49, 61) | 174 (135, 206) | – | 21 (21, 27) | 109 (78, 145) | – | – |
| 12–17 years | – | 21 (21, 27) | 187 (169, 205) | – | 21 (21, 26) | 105 (83, 143) | – | – |
| 18–40 years | – | 27 (21, 30) | 153 (112, 199) | – | 21 (21, 28) | 111 (86, 139) | – | – |

Data are presented as n (column %) unless indicated otherwise.
COVID-19, coronavirus disease; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

**Table 2**
Comparison of characteristics of patients with myocarditis/pericarditis within 30 days of receiving a COVID-19 vaccination or having first SARS-CoV-2 infection and the non-immunised population (reference group).

| | Homologous BNT162b2 vaccination | | | Heterologous prime-boost vaccination | | | Unvaccinated individuals | |
|---|---|---|---|---|---|---|---|---|
| | BNT162b2/BNT162b2/BNT162b2 | | | BBIBP-CorV/BBIBP-CorV/ BNT162b2 | | | First SARS-CoV-2 infection during the dominant Delta variant period | Non-immunised population(reference group) |
| | First dose | Second dose | Third dose | First dose | Second dose | Third dose | | |
| **Myocarditis** | | | | | | | | |
| Total number of individuals | (n = 61) | (n = 144) | (n = 10) | (n = 2) | (n = 0) | (n = 3) | (n = 18) | (n = 115) |
| **Sex** | | | | | | | | |
| Female | 19 (31.1) | 43 (29.9) | 3 (30) | 1 (50) | 0 (0) | 2 (66.7) | 7 (38.9) | 62 (53.9) |
| Male | 42 (68.9) | 101 (70.1) | 7 (70) | 1 (50) | 0 (0) | 1 (33.3) | 11 (61.1) | 53 (46.1) |
| **Age** | | | | | | | | |
| Mean age, years (SD) | 13.8 (2.7) | 14.3 (3.5) | 14.6 (2.4) | 22 (1.4) | – | 23.7 (8.1) | 21.2 (13.2) | 19.4 (10.9) |
| 5–11 years | 6 (9.8) | 5 (3.5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 7 (38.9) | 31 (27.0) |
| 12–17 years | 53 (86.9) | 134 (93.1) | 9 (90) | 0 (0) | 0 (0) | 0 (0) | 2 (11.1) | 39 (33.9) |
| 18–40 years | 2 (3.3) | 5 (3.5) | 1 (10) | 2 (100) | 0 (0) | 3 (100) | 9 (50) | 45 (39.1) |
| **Time between vaccination and onset** | | | | | | | | |
| Median interval (IQR), days | 3 (2, 10) | 3 (1, 3) | 2.5 (2, 3.8) | * | – | 5 (4, 12.5) | – | – |
| 24 h | 8 (13.1) | 40 (27.8) | 2 (20) | 0 (0) | 0 (0) | 0 (0) | – | – |
| 1–7 days | 35 (57.4) | 89 (61.8) | 6 (60) | 0 (0) | 0 (0) | 2 (66.7) | – | – |
| 8–30 days | 18 (29.5) | 15 (10.4) | 2 (20) | 2 (100) | 0 (0) | 1 (33.3) | – | – |
| **Hospital length of stay** | | | | | | | | |
| Median length (IQR), days | 3 (2, 5) | 3 (2, 5) | 3.5 (3, 6.5) | * | – | 7 (6.5, 8) | 9.5 (5.2, 15.5) | 7 (3.5, 11) |
| **Discharge status** | | | | | | | | |
| Alive | 61 (100) | 143 (99.3) | 10 (100) | 2 (100) | 0 (0) | 3 (100) | 16 (88.9) | 98 (85.2) |
| Dead | 0 (0) | 1 (0.7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (11.1) | 17 (14.8) |
| **Pericarditis** | | | | | | | | |
| Total number of individuals | (n = 16) | (n = 29) | (n = 2) | (n = 1) | (n = 1) | (n = 1) | (n = 2) | (n = 87) |
| **Sex** | | | | | | | | |
| Female | 3 (18.8) | 3 (10.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 33 (37.9) |
| Male | 13 (81.2) | 26 (89.7) | 2 (100) | 1 (100) | 1 (100) | 1 (100) | 2 (100) | 54 (62.1) |
| **Age** | | | | | | | | |
| Mean age, years (SD) | 14.8 (2.8) | 14.6 (2) | 15 (1.4) | * | * | * | 36 (4.2) | 26.5 (7.4) |
| 5–11 years | 1 (6.2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1.1) |
| 12–17 years | 14 (87.5) | 29 (100) | 2 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 12 (13.8) |
| 18–40 years | 1 (6.2) | 0 (0) | 0 (0) | 1 (100) | 1 (100) | 1 (100) | 2 (100) | 74 (85.1) |
| **Time between vaccination and onset** | | | | | | | | |
| Median interval (IQR) | 4.5 (3.8, 13.2) | 2 (1, 4) | * | * | * | * | – | – |
| 24 h | 1 (6.2) | 9 (31) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | – | – |
| 1–7 day | 10 (62.5) | 15 (51.7) | 2 (100) | 0 (0) | 0 (0) | 0 (0) | – | – |
| 8–30 day | 5 (31.2) | 5 (17.2) | 0 (0) | 1 (100) | 1 (100) | 1 (100) | – | – |
| **Hospital length of stay** | | | | | | | | |
| Median length (IQR), days | 3 (2, 4.2) | 2 (2, 5) | * | * | * | * | * | 5 (3,11) |
| **Discharge status** | | | | | | | | |
| Alive | 16 (100) | 29 (100) | 2 (100) | 1 (100) | 1 (100) | 1 (100) | 1 (50) | 84 (96.6) |
| Dead | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 | 0 (0) | 1 (50) | 3 (3.4) |

* As the sample size was too small, the calculation of statistical values was omitted.
Data are presented as n (column %) unless otherwise indicated.
COVID-19, coronavirus disease; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

pericarditis. Of the 220 cases of patients hospitalised with myocarditis within 30 days after vaccination, two-thirds (150/220) occurred after the second dose of BNT162b2 vaccine. Males (70.1 %) outnumbered females (29.9 %). Most cases of post-vaccination myocarditis occurred in adolescents aged 12–17 years, and were diagnosed 1–7 days after vaccination.

The median length of hospital stay in patients hospitalised with post-vaccination myocarditis was 3 days, whereas that of the patients with myocarditis after SARS-CoV-2 infection and in the reference group was 9.5 and 7 days, respectively. There was only one death due to myocarditis after two doses of BNT162b2 vaccine, compared with two and seventeen deaths in the SARS-CoV-2 infection and reference groups, respectively. There was only one death (0.7 %) due to post-two-dose BNT162b2 vaccination myocarditis, compared to two (11.1 %) and seventeen (14.8 %) cases in the SARS-CoV-2 infection and reference groups, respectively. Cases of hospitalised pericarditis showed a similar pattern, although the numbers were consistently lower across Table 2.

### 3.2. Myocarditis following vaccination

Figs. 2 and 3 show the number of myocarditis events per person-month (with a month equating to 30 days), and the IRRs for the homologous 3 × BNT162b2 (Fig. 2) vaccination and heterologous prime-boost vaccination with 2 × BBIBP-CorV/BNT162b2 (Fig. 3) for each immunisation status and age group among females and males. Overall, there was a significant increase in the incidence of myocarditis after homologous 3 × BNT162b2 vaccination, with IRRs of 3.09 (95 % CI: 1.61–5.93) in females and 7.43 (95 % CI: 3.11–17.73) in males. Considerable heterogeneity ($I^2$ > 50 %) was observed among the different age groups of males and females.

For the primary series of the BNT162b2 vaccine, the subgroup at the greatest risk of myocarditis was adolescent males who received the

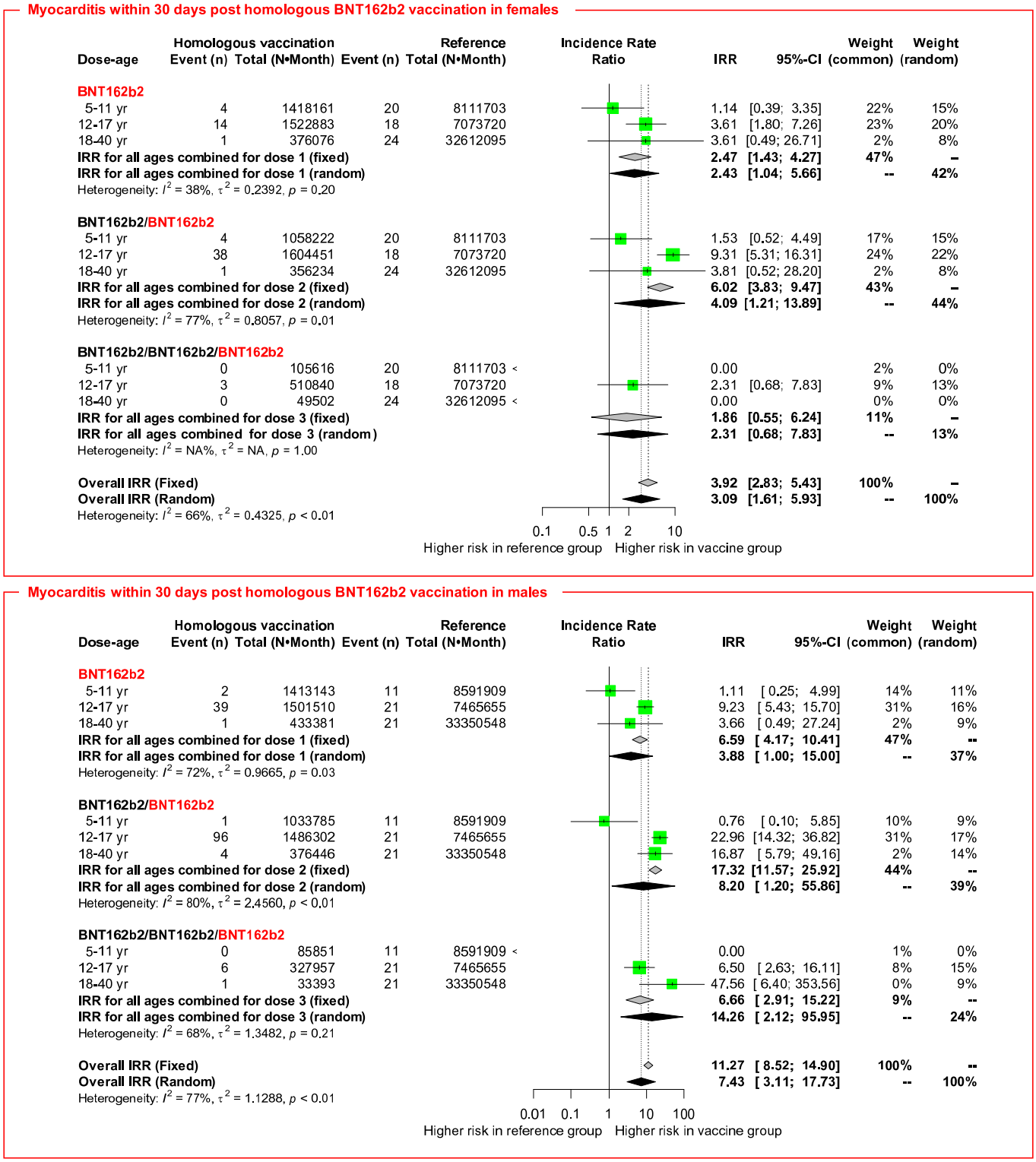


**Fig. 2.** Sex-specific incidence rates of myocarditis within 30 days after homologous three-dose 3 × BNT162b2 vaccination compared with those in the non-immunised population (reference group).Upper, females; lower, males; IRR, incidence rate ratio; CI, confidence interval.

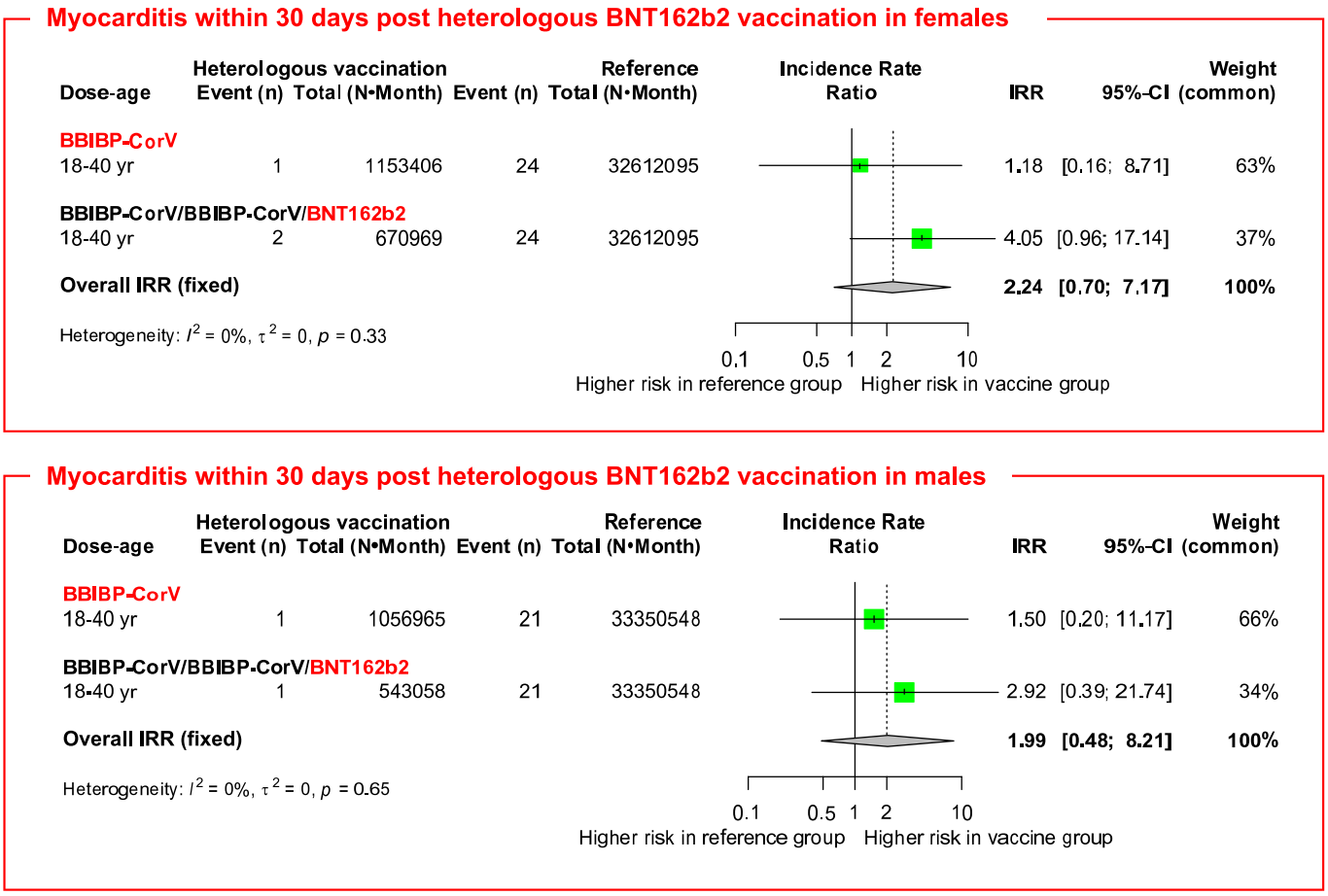


**Fig. 3.** Sex-specific incidence rates of myocarditis within 30 days after heterologous prime-boost vaccination with three-dose 2 × BBIBP-CorV/BNT162b2 compared with those in the non-immunised population (reference group).Upper, females; lower, males; IRR, incidence rate ratio; CI, confidence interval.The estimates for the 5–11 and 12–17 years age groups are not shown because no events were observed in these age groups.

second dose of the homologous BNT162b2 vaccine, exhibiting an IRR of 22.96 (95 % CI: 14.32–36.82). For the booster dose, the 95 % CIs of the IRRs were wider than those of the primary series due to a considerable reduction in sample size. There was no significant increase in the incidence of myocarditis after vaccination in females. However, the IRRs in males were significantly increased after vaccination, with an overall IRR of 14.26 (95 % CI: 2.12–95.95).

However, risk of myocarditis was not significantly increased in heterologous prime-boost vaccination group with 2 × BBIBP-CorV/BNT162b2. In the heterologous prime-boost vaccination group, the overall IRRs were 2.24 (95 % CI: 0.70–7.17) in females and 1.99 (95 % CI: 0.48–8.21) in males.

### 3.3. *Pericarditis following vaccination*

Figure S1 shows the incidence, person-months, and IRRs of hospitalised pericarditis following homologous 3 × BNT162b2 vaccination across various subgroups, paralleling the structure shown in Figs. 1–2. The risk of pericarditis was significantly increased among males, with an overall IRR of 10.48 (95 % CI: 3.90–28.15), but not among females. The overall IRR was not calculated for the heterologous prime-boost group with 2 × BBIBP-CorV/BNT162b2, because no cases of pericarditis occurred among males and only three cases occurred among females (Figure S2).

### 3.4. *Myocarditis and pericarditis following first SARS-CoV-2 infection*

Data obtained during the Delta variant-predominant period, revealed an overall IRR of 39.54 (95 % CI: 15.30–102.19) for myocarditis following the first SARS-CoV-2 infection among the unvaccinated individuals (Figure S3). Only two cases of pericarditis were observed following the first SARS-CoV-2 infection, of which both occurred in males.

## 4. Discussion

Our findings revealed that individuals aged 5–40 years showed a significantly increased incidence of myocarditis in individuals with homologous BNT162b2 vaccination and SARS-CoV-2 infection compared with the non-immunised population in the pre-COVID-19 period (reference group). The incidence of myocarditis within 30 days after vaccination was highest in males, typically following the second dose of the homologous 3 × BNT162b2 vaccination, with the 12–17-year age group being predominantly affected. After the third dose of BNT162b2 vaccine, the risk of myocarditis was significantly increased in males, but not in females. The risk for myocarditis was not significantly increased following any dose of the heterologous prime-boost 2 × BBIBP-CorV/BNT162b2 vaccination, but this finding is inconclusive owing to the limited statistical power.

We observed significant heterogeneity across the three age groups in the pooled IRR of myocarditis following any dose of the homologous 3 × BNT162b2 vaccine. Notably, children aged 5–11 years exhibited a lower risk of post-vaccination myocarditis, particularly after the first dose, compared with adolescents aged 12–17 years, and young adults aged 18–40 years. The IRR approaching 1 in children aged 5–11 years after the first dose of vaccine clearly suggests that they had a lower risk of

myocarditis. The difference in the cohort periods was attributable to the national vaccination policy. However, it is unlikely to be a cause of heterogeneity in the increased risk of myocarditis. In males, the risk of myocarditis differed between the 5–11 and 18–40-year age groups after the third dose of the homologous BNT162b2 vaccine, despite similar cohort periods across and sample sizes across different age groups.

The risk of pericarditis following homologous 3 × BNT162b2 vaccination, was markedly increased in male adolescents aged 12–17 years, the risk was not increased in females or other age groups. The incidence of pericarditis in females and after heterologous prime-boost 2 × BBIBP-CorV/BNT162b2 vaccination were too low to evaluate. The length of hospital stay and mortality rates in patients with post-vaccination myocarditis were generally lower than those with myocarditis in the SARS-CoV-2 infection and reference groups. Myocarditis in the reference group may have been caused by other viral infections or autoimmune diseases [28]. Our data also showed that the risk of myocarditis was higher after SARS-CoV-2 infection (Delta dominant) than the risk following vaccination.

The BNT162b2 vaccine, an mRNA-based vaccine, triggers the body to produce a large amount of the harmless segment of the SARS-CoV-2 spike protein, thereby eliciting an immune response [29]. However, there is a possibility that the spike protein could cross-react with proteins involved in heart muscle contraction [30,31]. The study results show that the incidence of myocarditis was higher following the administration of the BNT162b2 vaccine than after the BBIBP-CorV vaccine, an inactivated virus vaccine. This suggests that the BBIBP-CorV vaccine may lead to less exposure of the body to the spike protein [32]. We observed no significant risk of myocarditis risk after BBIBP-CorV vaccination in males aged 18–40 years; however, the risk of myocarditis was significantly elevated after any dose of the BNT162b2 vaccine in this age-sex group. The higher risk of myocarditis, longer hospital stays, and increased mortality in patients with SARS-CoV-2 infection, could be attributed to the ability of the SARS-CoV-2 spike protein to bind to angiotensin-converting enzyme 2 receptors in the heart muscle [33], which may be difficult to clear from the body, thereby increasing the likelihood of myocarditis.

Our findings align with the results of large studies conducted in Western countries, which indicate a higher risk of myocarditis and pericarditis, particularly among adolescent males, following BNT162b2 vaccination [6–12]. This was previously thought to be due to the increase in sex hormones in this age group [34,35]. In Thailand, the vaccination guidelines [16] considered evidence suggesting that extending the interval between doses could reduce the risk of myocarditis [13,36] in children aged 5–11 years. Therefore, no significant risk of myocarditis was observed in this age group for the second and third dose of the homologous 3 × BNT162b2 vaccination.

The increased risk of myocarditis observed after the third dose of the BNT162b2 vaccine aligns with findings from US studies, suggesting that the incidence of myocarditis/pericarditis after a booster dose of the homologous BNT162b2 vaccine may be similar to that after the first dose, and lower than that after the second dose of the primary series [9,11,12]. However, our study adds more information by comparing the incidence of myocarditis/pericarditis after vaccination with that in a reference population during the pre-COVID-19 period. Our study found that a heterologous prime-boost strategy with the 2 × BBIBP-CorV series, followed by the BNT162b2 vaccine, did not significantly increase the risk of myocarditis, even with a shorter interval between doses. However, this finding warrants further investigation.

The underlying mechanisms that result in some individuals developing pericarditis rather than myocarditis post-vaccination remain elusive [37]. Further research is required to elucidate the mechanisms, to enhance our understanding of these rare post-vaccination phenomena.

The primary strength of our study is the use of national population databases. This provided us with the unique advantage of including a population-based reference group, which significantly enhances the comparative integrity of our analysis. Given the background incidence of myocarditis and pericarditis in the non-immunised population, we conducted a historical control cohort study that showed an increased incidence of myocarditis and pericarditis following immunisation against the SARS-CoV-2.

A limitation of our study stems from the absence of data concerning immunogenic background [38] and other potential confounders such as health insurance status which could affect access to vaccination and healthcare for myocarditis. Due to limited data availability, our reference population in the pre-COVID-19 pandemic period was restricted to the period between August and October 2019. This brief period was insufficient to enable adjustment for seasonality and annual trends in myocarditis and pericarditis incidence. Moreover, our analysis only included cases of myocarditis and pericarditis that were sufficiently symptomatic to warrant hospitalisation, and did not include those that were asymptomatic and did not require hospitalisation. This could have led to an underestimation of IRRs in the vaccinated groups. However, this data gap is probably not of public health importance because asymptomatic cases typically do not impose a burden on public health resources. Furthermore, no conclusive evidence suggests detrimental long-term post-immunisation outcomes among individuals with asymptomatic myocarditis or pericarditis.

In the heterologous prime-boost vaccination with 2 × BBIBP-CorV/BNT162b2 cohort, the statistical power was limited in individuals younger than 18 years because of the limited sample size, thus limiting our ability to detect a significant increase in the incidence of myocarditis/pericarditis. The results of this study are difficult to interpret fully because of a lack of detailed biomolecular research. This highlights the need for further investigations in this field.

In conclusion, this study confirmed an increased risk of myocarditis following each dose of the homologous three-dose BNT162b2 vaccine and revealed that the risk of myocarditis following any dose of the BNT162b2 vaccine was still lower than that following SARS-CoV-2 infection (Delta variant) and was associated with a shorter hospital stay and lower mortality. We observed a significantly increased risk of pericarditis following the homologous vaccination in males. However, our study lacked the power to confirm an increased risk for myocarditis following heterologous prime-boost 2 × BBIBP-CorV/BNT162b2 vaccination. The incidence of pericarditis following the heterologous vaccination was too rare to evaluate.

## Data availability

The R codes and data for all analyses are available in a Jupyter notebook file which can be accessed through GitHub [39].

## CRediT authorship contribution statement

**Ponlagrit Kumwichar:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Virasakdi Chongsuvivatwong:** Investigation, Project administration, Supervision, Writing – review & editing. **Sanya Vasoppakarn:** Data curation, Resources, Writing – review & editing. **Narumol Atthakul:** Project administration, Writing – review & editing. **Vorthunju Nakhonsri:** Data curation, Writing – review & editing. **Chumpol Ngamphiw:** Data curation, Writing – review & editing, Resources. **Peerapat Khunkham:** Data curation, Resources, Writing – review & editing. **Watcharapot Janpoung:** Data curation, Resources, Writing – review & editing. **Sissades Tongsima:** Data curation, Resources, Writing – review & editing.

## Declaration of competing interest

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.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.026.

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