Heterologous third and fourth dose vaccine to reduce severity and mortality in COVID-19 patients during delta and omicron predominance: A cohort study in Chiang Mai, Thailand

Kannikar Intawong
Faculty of Public Health, Chiang Mai University
Suwat Chariyalertsak (suwat.c@cmu.ac.th)
Faculty of Public Health, Chiang Mai University
Kittipan Chalom
Chaiprakarn hospital, Chiang Mai Provincial Health Office
Thanachol Wonghirundecha
Chiang Mai Provincial Health Office
Woravut Kowatcharakul
San Sai Hospital, Chiang Mai Provincial Health Office
Pisittawoot Ayood
Wianghaeng Hospital, Chiang Mai Provincial Health Office
Aksara Thongprachum
Faculty of Public Health, Chiang Mai University
Narain Chotirosniramit
Faculty of Medicine, Chiang Mai University
Kajohnsak Noppakun
Faculty of Medicine, Chiang Mai University
Worachet Teacharak
Nakornping Hospital, Chiang Mai Provincial Health Office
Pimpinan khammawan
Nakornping Hospital, Chiang Mai Provincial Health Office

Research Article

Keywords: Heterologous vaccines, COVID-19, Severity, Death

Posted Date: August 26th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1973470/v1

Abstract

Background

The Coronavirus disease 2019 (COVID-19) pandemic has evolved quickly, with numerous waves of different variants of concern resulting in the need for countries to offer continued protection through booster vaccinations. To ensure adequate coverage, Thailand has proactively adopted heterologous vaccination schedules. While studies have assessed homologous schedules in detail, the effectiveness of heterologous booster vaccine schedules against severity and mortality of COVID-19 patients, particularly with newer variants, remains to be explored fully.

Methods

Utilising an active Hospital Information System for COVID-19 established in Chiang Mai, Thailand, we conducted a cohort study by linking patient-level data on laboratory-confirmed COVID-19 cases to the national immunization records, during delta-predominant (1st October – 31st December 2021) and omicron predominant (1st February – 30th April 2022) periods. Demographic and baseline clinical characteristics associated with severe COVID-19 outcomes and mortality were examined for each period.

Results

COVID-19 cases during delta predominance were ten times more likely to have severe outcomes and in-hospital deaths as compared to omicron predominance. During omicron predominance, a third vaccine dose was associated with 89% reduced risk of both severe COVID-19 and deaths, as compared to the unvaccinated group. Those who received the third dose 14–90 days prior to the date of positive SARS-CoV-2 test had the highest protection against severe COVID-19 outcomes (93%) followed by a drop to 87% among those who received their last dose > 90 days prior. Severe outcomes were not observed among third dose recipients during delta predominance and fourth dose recipients during omicron predominance. All the vaccine types used for boosting in Thailand offered similar protection against severe COVID-19.

Conclusions

The risk of severe outcomes were significantly lower for COVID-19 patients with omicron as compared to delta. Booster doses provided very high level of protection against severe COVID-19 outcomes and deaths. Ongoing booster campaigns should focus on improving coverage utilising all available vaccines to ensure optimal protection.

Background:

As of July 30th 2022, the Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 582 million confirmed cases globally with more than 170 million in Asia and almost 5 million in Thailand alone.[1] This has unfortunately resulted in almost 6.4 million deaths worldwide, 1.5 million deaths across Asia and over 31,000 deaths in Thailand.[1] While public health measures like wearing masks, social distancing and appropriate hygiene measures were able to limit the spread of SARS-CoV-2, the rapid development and deployment of vaccines was responsible for reducing the clinical impact of COVID-19 substantially.[2,3]

WHO has licensed 11 COVID-19 vaccines to date and globally almost 12 billion doses have been administered.[4] There are six approved COVID-19 vaccines in Thailand[5] and a sustained effort by the government has resulted in 76% of the population being fully vaccinated (2 doses) and an additional 43% receiving three doses or above as of 29th Jun 2022.[1,6] The rollout of vaccinations in Thailand started with inactivated vaccine (Sinovac) in March 2021[7] followed by ChAdOx1 (AstraZeneca) in June 2021[8] and BNT162b2 (Pfizer-BioNTech) in October 2021.[9] Due to challenges in vaccine supply and to manage public concerns around the effectiveness and duration of the inactivated vaccine, heterologous schedules were implemented in November 2021 including third dose (boosters) with ChAdOx1 and BNT162b2. The fourth doses (second booster) were administered widely beginning in January 2022, using BNT162b2, ChAdOx1 and mRNA-1273 (Moderna) in part to address additional concerns around potential immune escape by the omicron variant.

The initial clinical trials evaluated efficacy against early variants of concern, using homologous schedules, and high and equivalent effectiveness has been observed by the most widely used vaccines in real world studies, especially against severe COVID-19 outcomes.[10] Some studies have reported higher neutralizing-antibody response with heterologous boosters as compared to homologous boosters.[11–13] However, there is limited data available on the protective benefit of heterologous schedules, particularly against newer variants of concern.[14,15] Currently, the prevalent Omicron variant is reported to have increased transmissibility but lower clinical severity as compared to previous variants,[16–18] and studies report reduced vaccine effectiveness against Omicron infection.[16,19] While Omicron is assumed to have decreased clinical severity compared to earlier variants, this has also occurred in a background of higher vaccination coverage and increased exposure to natural infection, both of which will elevate individual and community level protection from disease and may have contributed to the perception of Omicron as a milder variant. Recent accounts of significant mortality due to Omicron in elderly, under-vaccinated populations suggests omicron per se, may not be as mild as we think.[20,21] Irrespective of whether the clinical severity of the Omicron variant is lower or not in the overall population, there exists a subgroup of high-risk individuals, who are older, immunocompromised and with pre-existing chronic medical conditions, who remain vulnerable to severe outcomes following SARS-CoV-2 infection.[22–24] It is important to characterise this subgroup and understand how the reduced vaccine effectiveness impacts severe outcomes, in a background of heterologous boosting. This becomes even more relevant for Asian countries where heterologous schedules have been used very widely.

Utilising a unique hospital information system (HIS) network established in Chiang Mai, Thailand, we aimed to assess the role of heterologous vaccination schedules on risk of severe COVID-19 outcomes and death among COVID-19 patients during omicron and delta predominant periods.

Methods:

Study population:

The current study draws on an active HIS network established in Chiang Mai, located in Northern Thailand, with a population of 1.6 million. Adult patients with confirmed COVID-19 during October – December 2021 and February– April 2022 time periods were included in the study. Molecular testing revealed 96.5% delta and 95.6% omicron lineage during 1st Oct 2021 – 31st Dec 2021 and 1st Feb 2022 – 30th Apr 2022 periods, respectively. Patients with tests done in Jan 2022 were excluded due to mixed delta-omicron lineage among samples (Omicron 75%, Delta 25%).

Non-Thai residents and migrants were excluded as the vaccination data and outcome capture for this group may be incomplete. Patients with missing age were also excluded. The patient selection flow is presented under **Figure 1**.

Data Sources:

We have previously published the details on creating and implementing the information systems used in this study.[25] In brief, all COVID-19 cases detected in Chiang Mai province are reported into the hospital information system of Chiang Mai Provincial Health Office (CMC-19 HIS), under the Communicable Disease Control Act (B.E. 2558) which mandates national reporting of all COVID-19 cases. CMC-19 HIS is a web-based reporting system which was launched since April 2021 and was created by Chiang Mai Provincial Health Office and Faculty of Public Health of Chiang Mai University. When a COVID-19 case is detected, the healthcare staff enter the patient details, including laboratory results into the CMC-19 HIS under a unique individual ID and this platform is also used for bed management in the overall province. The criteria for hospitalization were different during delta and omicron periods. Even mild cases who test positive for SARS-CoV-2 were admitted to hospital and remained for at least 7 days in hospital during delta period whereas asymptomatic or mild cases were treated as out-patient and isolated in designated places in community, community-isolation, or home-isolation since the beginning of omicron period. Data on severity and progression of the disease including requirement of ventilatory support and treatments are recorded in each hospital's information system. Death cases reported to Chiang Mai Provincial Health Office are routinely updated in CMC-19 HIS.

All national vaccination records are available from the Ministry of Public Health Immunization Center (*MOPH IC*) database and deposited in the "Morprom" application, maintained by the Ministry of Public Health, Thailand.

Ethical considerations:

The study was conducted on routine data collected as part of the national COVID-19 response under the Communicable Disease ACT (B.E. 2558) and was exempted from ethics review. Data were de-identified at source and analysed by Chiang Mai Provincial Health Office and Faculty of Public Health, Chiang Mai University.

Study Design:

We conducted a retrospective cohort study on Thai residents aged 18 years or older, with laboratory confirmed SARS-CoV-2 infection during 1st October – 31st December 2021 (Delta predominant) and 1st February– 30th April 2022 (Omicron predominant) time periods. Date of first positive SARS-CoV-2 test served as the index (baseline) date. If two positive SARS-CoV-2 tests were available for the same individual >90days apart, the second was considered a reinfection and the earlier episode was included in the analysis. Reinfections accounted for <0.01% of the total cohort.

Demographic data, baseline clinical characteristics were extracted from the CMC-19 hospital management platform. The types of COVID-19 vaccines, and dates of vaccinations were extracted from MOPH-IC immunization database.

Severe COVID-19 outcome was defined as requiring Invasive Mechanical Ventilation (IMV) during hospital admission or death during hospital admission. Records of all included subjects were followed till death, or up to 30 days from first positive SARS-CoV-2 test. The severe outcome capture for the study population is near complete as the clinical information of all hospitalised COVID-19 cases of the 26 public and 8 private hospitals in Chiang Mai province, including the only two tertiary care referral hospitals in Chiang Mai, are entered into a single CMC-19 HIS platform.

Statistical Analysis:

Descriptive statistics are reported separately for the subjects with and without severe COVID-19, stratified by delta and omicron predominance. A separate comparison was done comparing subjects during delta predominance as compared to omicron predominance to understand how the clinical characteristics and other risk factors differed between the periods. Continuous variables are summarized as mean and standard deviation (SD) or median and interquartile range (IQR) depending on the distribution. Categorical variables are summarized as frequency and percentages. Between group comparisons were done using Mann-Whitney-U test or t-test for continuous variables and Chi-squared test or Fisher's exact test for categorical variables.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) for severe COVID-19 and mortality outcomes, separately for omicron and delta predominance. Follow up period was taken from the first positive SARS-CoV-2 test date and censored at the earliest of: severe COVID-19 (either death or IMV), date of discharge for hospitalised or 30 days from first positive SARS-CoV-2 test date. If the outcome occurred on the first positive SARS-CoV-2 test date, the follow-up time was taken to be 0.5 days. Age, gender, calendar day of test (in weekly units), vaccination status and schedules, and time since last

vaccine were added as factors in the regression model to estimate adjusted HRs (95% CI) for severe COVID-19 and mortality outcomes.

All statistical analyses were be conducted using stata (version 15.0 SE, College station, TX:StataCorp LP). Significance tests are 2 sided and a p-values <0.05 was considered statistically significant.

Results:

Baseline clinical characteristics

There were 26,481 COVID-19 patients during the delta predominant period (1 October 2021 to 31 December 2021), and 265,677 COVID-19 patients during the omicron predominant period (1 Feb 2022 to 30 Apr 2022), in Chiang Mai province. After applying the exclusion criteria, 17,047 (64%) and 188,043 (71%) Thai residents above 18 years of age were included in the final analysis for the delta and omicron predominant periods respectively (Fig. 1).

During delta predominance, COVID-19 patients were more likely to be male as compared to omicron predominance (49% vs 45%), while the median age during both periods was 38 years. As compared to omicron predominance, patients during delta predominance were ten times more likely to have severe COVID-19 outcomes (0.10% vs 1.13%), undergo IMV (0.06% vs 0.76%) and have in-hospital deaths (0.06% vs 0.76%) (Table 1).

Table 1
Comparison of clinical characteristics of COVID-19 patients during Delta predominance (1 Oct – 31 Dec 2021) with Omicron predominance (1 Feb – 30 Apr 2022) in Chiang Mai, Thailand

N = 205,090	**Delta predominance**	**Omicron predominance**	
Variable			*p-value*
Number	**17,047**	**188,043**	-
Age, years			
Mean (SD)	40 (16)	41 (17)	
Median (IQR)	38 (27–52)	38 (27–54)	*0.10*
Age group, n(%)			
18–29	5335 (31.3)	58585 (31.2)	*< 0.01*
30–39	3774 (22.1)	40442 (21.5)	
40–49	3085 (18.1)	31217 (16.6)	
50–59	2341 (13.7)	26106 (13.9)	
60–69	1655 (9.7)	21542 (11.5)	
≥ 70	857 (5.1)	10151 (5.4)	
Gender, n(%)			
Female	8742 (51.3)	103852 (55.2)	*< 0.01*
Male	8305 (48.7)	84191 (44.8)	
COVID-19 outcomes			
Severe COVID-19, n(%)	192 (1.13)	195 (0.10)	*< 0.01*
IMV, n(%)	130 (0.76)	117 (0.06)	*< 0.01*
Median (IQR) time from first positive test to IMV, days	4 (1–8)	1 (0–6)	*< 0.01*
In-hospital deaths, n(%)	129 (0.76)	121 (0.06)	*< 0.01*
Median (IQR) time from first positive test to death, days	12 (7–18)	8 (3–13)	*< 0.01*
Vaccination Status, n(%)			
Unvaccinated	6338 (37.2)	16372 (8.7)	*< 0.01*
Vaccinated One dose	3374 (19.8)	2968 (1.6)	

N = 205,090	**Delta predominance**	**Omicron predominance**	
Vaccinated two doses	6843 (40.1)	96382 (51.3)	
Vaccinated three doses	492 (2.9)	65492 (34.8)	
Vaccinated four doses	0 (0)	6829 (3.6)	
Type of primary vaccine series, n(%)	**n = 6843**	**n = 96382**	
Sinovac/ Sinopharm-ChAdOx1	3071 (44.9)	39553 (41.0)	*< 0.01*
Sinovac- Sinovac or SP-SP	2840 (41.5)	13522 (14.0)	
ChAdOx1- ChAdOx1	650 (9.5)	2845 (2.9)	
Pfizer- Pfizer	87 (1.3)	10615 (11.0)	
ChAdOx1- Pfizer/Moderna	178 (2.6)	25711 (26.7)	
Sinovac/Sinopharm - Pfizer /Moderna	13 (0.2)	464 (0.5)	
Moderna-Moderna	4 (0.05)	3672 (3.8)	
Type of third vaccine dose, n(%)	**n = 492**	**n = 65492**	
Pfizer-BioNTech	187 (38.0)	31589 (48.2)	*< 0.01*
ChAdOx1 (AstraZeneca)	231 (47.0)	20313 (31.0)	
Moderna	68 (13.8)	13531 (20.7)	
Other	6 (1.2)	59 (0.1)	
Type of fourth vaccine dose, n(%)	**n = 0**	**n = 6829**	
Pfizer-BioNTech		3277 (47.9)	-
ChAdOx1 (AstraZeneca)		511 (7.5)	
Moderna		3032 (44.4)	
Other		9 (0.1)	
Median (IQR) time since last vaccination, days	28 (13–64)	92 (62,126)	*< 0.01*
Time since last vaccination, n(%)	**n = 10709**	**n = 171671**	
≤ 14days	2979 (27.8)	6289 (3.7)	
> 14–90 days	6520 (60.9)	76696 (44.7)	
> 90–180 days	1183 (11.1)	80013 (46.6)	
> 180 days	27 (0.2)	8673 (5.0)	

N = 205,090	Delta predominance	Omicron predominance
IMV = Invasive Mechanical Ventilation		

Patients during delta predominance were more likely to have received ChAdOx1 as third vaccine dose while those during omicron predominance were more likely to have received Pfizer-BioNTech or Moderna, which is reflective of the booster dose roll-out in Thailand.[6] The majority of patients during omicron predominance had their last vaccination > 90 days ago, whereas the majority of those during delta predominance had their last vaccination between 14–90 days **(**Table 1**).**

Severe COVID-19 outcomes

Severe COVID-19 outcomes and deaths were observed in 192 (1.13%) and 129 (0.76%) patients during delta predominance, and 195 (0.1%) and 121 (0.06%) patients during omicron predominance, respectively. Patients with severe outcomes were on average, over 30 years older than those without severe outcomes, with over 70% aged 60 years or older, during both periods **(Supplementary Fig. 1)**. Patients with severe outcomes were more likely to be male, with 54% and 62% of those with severe outcomes being male during delta and omicron predominance, respectively. **(**Table 2**).**

Table 2
Comparison of clinical characteristics of COVID-19 patients with and without severe outcomes during Delta predominance (1 Oct – 31 Dec 2021) and Omicron predominance (1 Feb – 30 Apr 2022) in Chiang Mai, Thailand

	Delta predominance (N = 17047)			**Omicron predominance (N = 188,043)**		
Variable	**With severe COVID-19 outcome**	**Without severe COVID-19 outcome**	p-value	**With severe COVID-19 outcome**	**Without severe COVID-19 outcome**	p-value
Number (%)	192 (1.13)	16855 (98.87)	-	195 (0.1)	187848 (99.9)	
Age, years						
Mean (SD)	67 (15)	40 (16)		68 (17)	41 (16)	
Median (IQR)	67 (57–80)	38 (27–51)	*< 0.01*	71 (59–82)	38 (27–54)	*< 0.01*
Age group, n(%)						
18–29	2 (1.0)	5333 (31.6)	*< 0.01*	8 (4.1)	58577 (31.2)	*< 0.01*
30–39	6 (3.1)	3768 (22.4)		7 (3.6)	40435 (21.5)	
40–49	13 (6.8)	3072 (18.2)		11 (5.6)	31206 (16.6)	
50–59	35 (18.2)	2306 (13.7)		26 (13.3)	26080 (13.8)	
60–69	51 (26.6)	1604 (9.5)		39 (20.0)	21503 (11.4)	
≥ 70	85 (44.3)	772 (4.6)		104 (53.4)	10047 (5.4)	
Gender, n(%)						
Male	104 (54.2)	8201 (48.7)	*< 0.01*	120 (61.5)	84071 (44.8)	*< 0.01*
Female	88 (45.8)	8654 (51.3)		75 (38.5)	103777 (55.2)	
Vaccination Status, n(%)						

Adjusted for gender and calendar time. Reference group: Unvaccinated

Adjusted for age, gender and calendar time. Reference group: Unvaccinated

	Delta predominance (N = 17047)			Omicron predominance (N = 188,043)		
Unvaccinated	148 (77.1)	6190 (36.7)	< *0.01*	103 (52.8)	16269 (8.7)	< *0.01*
Vaccinated One dose	28 (14.6)	3346 (19.9)		6 (3.1)	2962 (1.6)	
Vaccinated two doses	16 (8.3)	6827 (40.5)		62 (31.8)	96320 (51.3)	
Vaccinated three doses	0 (0)	492 (2.9)		24 (12.3)	65468 (34.9)	
Vaccinated four doses				0 (0)	6829 (3.6)	
Type of primary vaccine series, n(%)	**n = 16**	**n = 6827**		**n = 62**	**n = 96320**	
Sinovac/ Sinopharm-ChAdOx1	8 (50.0)	3063 (44.9)	-	14 (22.6)	39539 (41.1)	*0.010*
Sinovac- Sinovac or SP-SP	3 (18.8)	2837 (41.6)		8 (12.9)	13514 (14.0)	
ChAdOx1- ChAdOx1	4 (25.0)	646 (9.5)		6 (9.7)	2839 (2.9)	
Pfizer- Pfizer	0 (0)	87 (1.3)		7 (11.3)	10608 (11.0)	
ChAdOx1- Pfizer/Moderna	1 (6.2)	177 (2.6)		24 (38.7)	25687 (26.7)	
Sinovac/Sinopharm - Pfizer /Moderna	0 (0)	1 (0.01)		0 (0)	464 (0.5)	
Moderna-Moderna	0 (0)	3 (0.04)		3 (4.8)	3669 (3.8)	
Type of third vaccine dose, n(%)	**n = 0**	**n = 492**		**n = 24**	**n = 65468**	
Pfizer-BioNTech		187 (38.1)	-	12 (50.0)	31577 (48.2)	*0.967*
ChAdOx1 (AstraZeneca)		231 (46.9)		8 (33.3)	20305 (31.0)	
Moderna		68 (13.8)		4 (16.7)	13527 (20.7)	
Other		6 (1.2)		0 (0)	59 (0.1)	
Adjusted for gender and calendar time. Reference group: Unvaccinated						
Adjusted for age, gender and calendar time. Reference group: Unvaccinated						

	Delta predominance (N = 17047)			Omicron predominance (N = 188,043)		
Type of fourth vaccine dose, n(%)	**n = 0**	**n = 0**		**n = 0**	**n = 6829**	
Pfizer-BioNTech					3277 (47.9)	-
ChAdOx1 (AstraZeneca)					511 (7.5)	
Moderna					3032 (44.4)	
Other					9 (0.1)	
Median (IQR) time since last vaccination, days	18 (6–38)	28 (13–64)	*0.578*	95 (64–143)	92 (62–126)	*0.580*
Time since last vaccination, n(%)	**n = 44**	**n = 10665**		**n = 92**	**n = 171579**	
≤ 14days	19 (43.2)	2960 (27.8)	*0.107*	7 (7.6)	6282 (3.7)	*< 0.01*
> 14–90 days	23 (52.3)	6497 (60.9)		37 (40.2)	76659 (44.7)	
> 90–180 days	2 (4.6)	1181 (11.1)		36 (39.1)	79977 (46.6)	
> 180 days	0 (0)	27 (0.2)		12 (13.0)	8661 (5.0)	
Adjusted for gender and calendar time. Reference group: Unvaccinated						
Adjusted for age, gender and calendar time. Reference group: Unvaccinated						

During delta predominance 77% of patients with severe outcomes were unvaccinated, as compared to 37% without severe outcomes. During omicron predominance > 50% of patients with severe outcomes were unvaccinated as compared to just 9% without severe outcomes. For both periods, patients who received at least one booster dose had very few events **(Supplementary Fig. 1)**. Among the vaccinated, patients with severe outcomes during omicron predominance were more likely to have received the last dose either < 14 days or > 180 days from date of positive test **(**Table 2**).**

Among the COVID-19 patients who had received a third vaccine dose during delta predominance, 47%, 38% and 14% had received ChAdOx1, Pfizer-BioNTech and Moderna respectively. In a sample of residents tested at a community COVID-19 testing facility during the same period, the distribution was 73%, 18% and 9% for ChAdOx1, Pfizer-BioNTech and Moderna respectively. [26] Severe outcomes were not observed in those who have received a third dose indicating that that all vaccine types used as third dose offered potentially complete protection against severe outcomes during delta predominance.

The vaccine types used for third booster did not differ significantly between patients with and without severe outcomes during omicron predominance. Among those who had received a fourth vaccine dose, 8%, 48% and 44% of patients received ChAdOx1, Pfizer-BioNTech and Moderna respectively. In a sample of residents tested at a community COVID-19 testing facility during the same period, the distribution was 6%, 50% and 43% ChAdOx1, Pfizer-BioNTech and Moderna respectively. [26] Severe outcomes were not observed in those who received a fourth dose indicating that all vaccine types used as fourth dose offer potentially complete protection against severe outcomes due to Omicron.

Factors associated with severe COVID-19 outcomes and mortality

During both delta and omicron predominance older age and male gender were associated with significantly higher risk of both severe COVID-19 and mortality even after adjusting for calendar time and number of vaccines received **(Supplementary Table 1a and 1b)**

During delta predominance, severe outcomes or deaths were not observed among patients who received a third dose after a median of 51 (IQR 12–95) days since the last vaccine dose. After adjusting for age, gender and calendar time of test, receiving the primary vaccination series was associated with 87% and 89% reduction of risk of severe COVID-19 and mortality, respectively as compared to the unvaccinated group. In age stratified adjusted models, receiving the primary vaccination series was associated with a 91% risk reduction among 50–69 years age group and 86% risk reduction among ≥ 70 year age group, for both severe COVID-19 and mortality **(Supplementary Fig. 2 and Supplementary Table 1a).** Those who received the primary series 14–90 days prior to the date of positive SARS-CoV-2 test had the highest risk reduction against severe COVID-19 outcomes (88%). Among those who received at least one vaccine dose, risk reduction was 46% for ≤ 14 days, 56% for 14–90 days while no protection was offered after 90 days **(Supplementary Table 1a).**

During omicron predominance, severe outcomes or deaths were not observed among patients who received a fourth dose after a median of 53 (IQR 29–75) days since the last vaccine dose. After adjusting for age, gender and calendar time of test, receiving a third dose was associated with 89% reduction of risk of severe COVID-19 (HR 0.11, 95% CI 0.07–0.11) and mortality (HR 0.11, 95% CI 0.06–0.21), as compared to the unvaccinated group, while receiving only the primary series was associated with 80% risk reduction **(Supplementary Table 1b).** The protection offered against severe COVID-19 outcomes did not differ significantly across age groups **(**Fig. 2**).** All three vaccine types used for boosting, ChAdOx1, Pfizer-BioNTech and Moderna, offered similar protection against severe COVID-19 **(Supplementary Fig. 3).**

Patients who received the third dose 14–90 days prior to the date of positive SARS-CoV-2 test had the highest risk reduction against severe COVID-19 outcomes (93%) followed by > 90 days (87%) and ≤ 14 days (83%). Similarly, those who received the primary series 14–90 days had the highest risk reduction (85%), and waning was observed > 90days (76%) and > 180days (70%). Receiving the primary series ≤ 14 days was not protective against severe outcomes during omicron predominance **(Supplementary Table 1b**, Fig. 3**).**

Discussion:

While the number of COVID-19 cases and deaths globally is unacceptably high, the impact of vaccinations is undisputable, when they have been implemented appropriately. As vaccination schedules have rapidly evolved to third and fourth doses in an attempt to manage new variants and concerns around waning immunity, the availability of data to support decision makers has struggled to keep pace. The current study provides urgently needed data to support the continued rollout of booster dose schedules in Thailand and Asia and for the first time provides data for fourth dose schedules incorporating inactivated vaccines into the primary series.

Our results confirm the findings from other groups that the omicron variant appears to be associated with lower clinical severity as compared to delta variant [16–18] We observed ten times lower rate of mortality and IMV use, which is consistent with values previously reported. However, it should be noted that prior vaccination coverage and prior exposure to natural infection is likely to be considerably higher at a population level during the Omicron period, as compared to the delta period. This will inevitably bias the protection observed in real world studies, potentially contributing to the perception that omicron is much milder clinically than the reality may actually be.

Our study found ~ 90% reduced risk of severe outcomes with omicron among patients who had received a third dose as compared to unvaccinated patients. The level of protection with a third dose observed in our study is comparable to observations from Norway[17], UK[16] and Denmark.[18] Severe outcomes or deaths were not observed among third dose recipients during delta predominance or fourth dose recipients during omicron predominance, indicating that timely boosting provides very high level of protection against severe COVID-19 outcomes irrespective of the variant type. However, in the current study we were unable to examine other confounders such as chronic comorbidities which are important risk factors of severe COVID-19 outcomes and deaths.

We observed some waning of the protective effect of booster doses on severe COVID-19 outcomes with optimal protection observed with both two and three dose vaccines 14–90 days from the last vaccine dose. The risk reduction dropped by 9% and 15% at > 90 days and > 180 days respectively for two dose regime and by 6% at > 90days for the three-dose regime. Although multiple studies have reported on waning effectiveness of vaccines over time against infection, there are limited studies examining this against severe COVID-19 and mortality. A study from US-CDC found that among recipients of three doses, effectiveness against COVID-19–associated hospitalizations declined from 91% among those vaccinated within the past 2 months to 78% among those vaccinated ≥ 4 months earlier.[27] A similar finding was observed in a study among long term care residents, where waning of booster doses against mortality appeared around fourth month and continued to decline over coming months.[28] These findings indicate that although protection decreased with time, a booster dose was still highly effective at preventing severe illness with COVID-19.

Our study found that the three vaccine types used for boosting in Thailand, ChAdOx1, Pfizer-BioNTech and Moderna, offered similar protection against severe COVID-19 outcomes.. Comparable protection from ChAdOx1 and Pfizer-BioNTech against infection has been previously reported.[10,16]

Our data strongly suggests that accelerating the third and fourth dose vaccinations and increasing coverage by using any vaccines available, particularly among those aged 60 and older or those with co-morbidities is an important strategy to optimize protection. Vaccination in addition to using personal protection measures such as wearing a mask, social distancing, and avoiding crowded settings, can help to reduce hospitalizations associated with omicron strain and, more importantly, mortality in the elderly or those with co-morbidities.

Conclusions And Forward View:

Despite improving vaccine coverage in many countries including Thailand, infections due to the omicron variant (and sub-variants) continue to occur. This has led to concerns around waning protection, and many studies have confirmed a more rapid waning of protection against infection with omicron than for earlier variants, driving the introduction of booster doses, as a third and now fourth vaccination dose. Importantly, we continue to see very high levels of protection against serious outcomes. The current study confirms a complete primary series provides up to 80% protection against severe outcomes due to Omicron, while a third dose increases that to almost 90% and a fourth dose potentially eliminates that risk completely. One important gap in our current knowledge here though, relates to the duration of this enhanced protection with booster doses. The longest follow up we have in our cohort is 75 days with a median of 53 days after the fourth dose. Defining the way forward is still not clear as understanding this duration of protection is critical to recommendations relating to the frequency of future booster doses.

Additionally, the current study uses population level cohort data and we know that vaccine effectiveness is reduced in higher risk segments of society, such as the elderly and immunocompromised. Any recommendations relating to the frequency of booster doses may not be universally applicable to these groups, inferring a more targeted approach to vaccination programmes in the future. One question that the current study can address with confidence, is the issue of which vaccine provides optimal protection. Our data demonstrates comparable protection by each of the vaccines used as booster doses in Thailand, irrespective of the primary series that preceded them. This strongly supports the use of ChAdOx1 (AstraZeneca), Pfizer-BioNTech and Moderna as booster vaccines, providing much needed flexibility to incorporate different vaccines into schedules according to local supply and logistical considerations.

Declarations

Acknowledgements:

This research was supported by the National Research Council of Thailand (NRCT) under The Smart Emergency Care Services Integration (SECSI) project to Faculty of Public Health Chiang Mai University. We are grateful to the Chiang Mai Provincial Health Office and the Department of Disease Control Ministry of Public Health for the collaborative partnerships in managing health information of COVID-19 epidemic.

References

1. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus Pandemic (COVID-19). Published online at https://ourworldindata.org/coronavirus. [Last accessed 31 July 2022].
2. Doroshenko A. The Combined Effect of Vaccination and Nonpharmaceutical Public Health Interventions—Ending the COVID-19 Pandemic. *JAMA Netw Open* 2021;4(6):e2111675.
3. Moore Sï»¿, Hill EM, Tildesley MJ, Dyson L, Keeling MJ, et alï»¿. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. Lancet Infect Dis 2021;S1473-3099(21)00143-2. Published online March 18, 2021. doi:10.1016/S1473-3099(21)00143-2.
4. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2022. Available online at https://covid19.who.int/. [Last accessed 21 July 2022].
5. Thailand Food and Drug Administration: Medicines Regulation Division, 2022. Available online at https://www.fda.moph.go.th/sites/drug/SitePages/Vaccine_SPC-Name.aspx. [Last accessed 21 July 2022].
6. Thailand Department of Disease Control, Available from: https://ddc.moph.go.th/dcd/pagecontent.php?page=994&dept=dcd. [Last accessed 21 July 2022].
7. Palacios R, Batista AP, Albuquerque CSN, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. Available online at https://ssrn.com/abstract=3822780. [Last accessed 21 July 2022].
8. Voysey M, Costa Clemens SA, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111.
9. Polack FP, Thomas SJ, Kitchin N, et al. C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
10. Chuenkitmongkol S, Solante R, Burhan E, et al. Expert Review on global real-world vaccine effectiveness against SARS-CoV-2. Exp Rev Vacc 2022. doi: 10.1080/14760584.2022.2092472.
11. Atmar RL, Lyke KE, Deming ME, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med 2022;386:1046–1057.
12. Barros-Martins J, Hammerschmidt SI, Cossmann A, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med 2021;27:1525–1529.

13. Liu X, Shaw RH, Stuart ASV, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet 2021;398:856–869.
14. Mayr FB, Talisa VB, Shaikh O, Yende S, Butt AA, et al. Effectiveness of homologous or heterologous Covid-19 boosters in veterans. N Engl J Med 2022;386:1375–1377.
15. Accorsi EK, Britton A, Shang N, et al. Effectiveness of Homologous and Heterologous Covid-19 Boosters against Omicron. N Engl J Med 2022. Available from https://www.nejm.org/doi/full/10.1056/NEJMc2203165. [Last accessed 21 June 2022].
16. Nyberg, Tommy et al. “Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study.” Lancet (London, England) vol. 399,10332 (2022): 1303–1312. doi:10.1016/S0140-6736(22)00462-7
17. Veneti L, Bøås H, Bråthen Kristoffersen A, et al. Reduced risk of hospitalisation among reported COVID-19 cases infected with the SARS-CoV-2 omicron BA.1 variant compared with the delta variant, Norway, December 2021 to January 2022. Eurosurveillance 2022; 27: 2200077.
18. Bager, Peter et al. Risk of hospitalisation associated with infection with SARS-CoV-2 omicron variant versus delta variant in Denmark: an observational cohort study. The Lancet. Infectious diseases vol. 22,7 (2022): 967–976. doi:10.1016/S1473-3099(22)00154-2
19. Andrews N, Stowe J, Kiresbom F, et al. Effectiveness of COVID-19 vaccines against the omicron (B.1.1.529) variant of concern. NEJM 2022. doi:10.1056/NEJMoa2119451.
20. Taylor, Luke. “Covid-19: Hong Kong reports world's highest death rate as zero covid strategy fails.” BMJ (Clinical research ed.) vol. 376 o707. 17 Mar. 2022, doi:10.1136/bmj.o707
21. Taiwan Centres for Disease Control. COVID-19 dashboard. Available online at https://www.cdc.gov.tw/En. [Last accessed 08 Aug 2022].
22. Whitaker, Heather J et al. “Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response amongst individuals in clinical risk groups.” The Journal of infection vol. 84,5 (2022): 675–683. doi:10.1016/j.jinf.2021.12.044
23. Agrawal, Utkarsh et al. “COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): a prospective cohort study.” The Lancet. Respiratory medicine vol. 9,12 (2021): 1439–1449. doi:10.1016/S2213-2600(21)00380-5
24. E.J. Williamson, A.J. Walker, K. Bhaskaran, et al. Factors associated with COVID-19-related death using OpenSAFELY Nature, 584 (7821) (2020), pp. 430–436
25. Intawong K, Olson D, Chariyalertsak S. Application technology to fight the COVID-19 pandemic: Lessons learned in Thailand. Biochem Biophys Res Commun 2021;534:830–836.
26. Suwat Chariyalertsak, Kannikar Intawong, Kittipan Chalom et al. ï»¿Effectiveness of heterologous 3rd and 4th dose COVID-19 vaccine schedules for SARS-CoV-2 infection during delta and omicron predominance in Thailand., 28 June 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1792139/v1]

27. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:255–263. DOI: http://dx.doi.org/10.15585/mmwr.mm7107e2external icon
28. Nordström, Peter et al. “Effectiveness of a fourth dose of mRNA COVID-19 vaccine against all-cause mortality in long-term care facility residents and in the oldest old: A nationwide, retrospective cohort study in Sweden.” The Lancet regional health. Europe, 100466. 13 Jul. 2022, doi:10.1016/j.lanepe.2022.100466

Figures

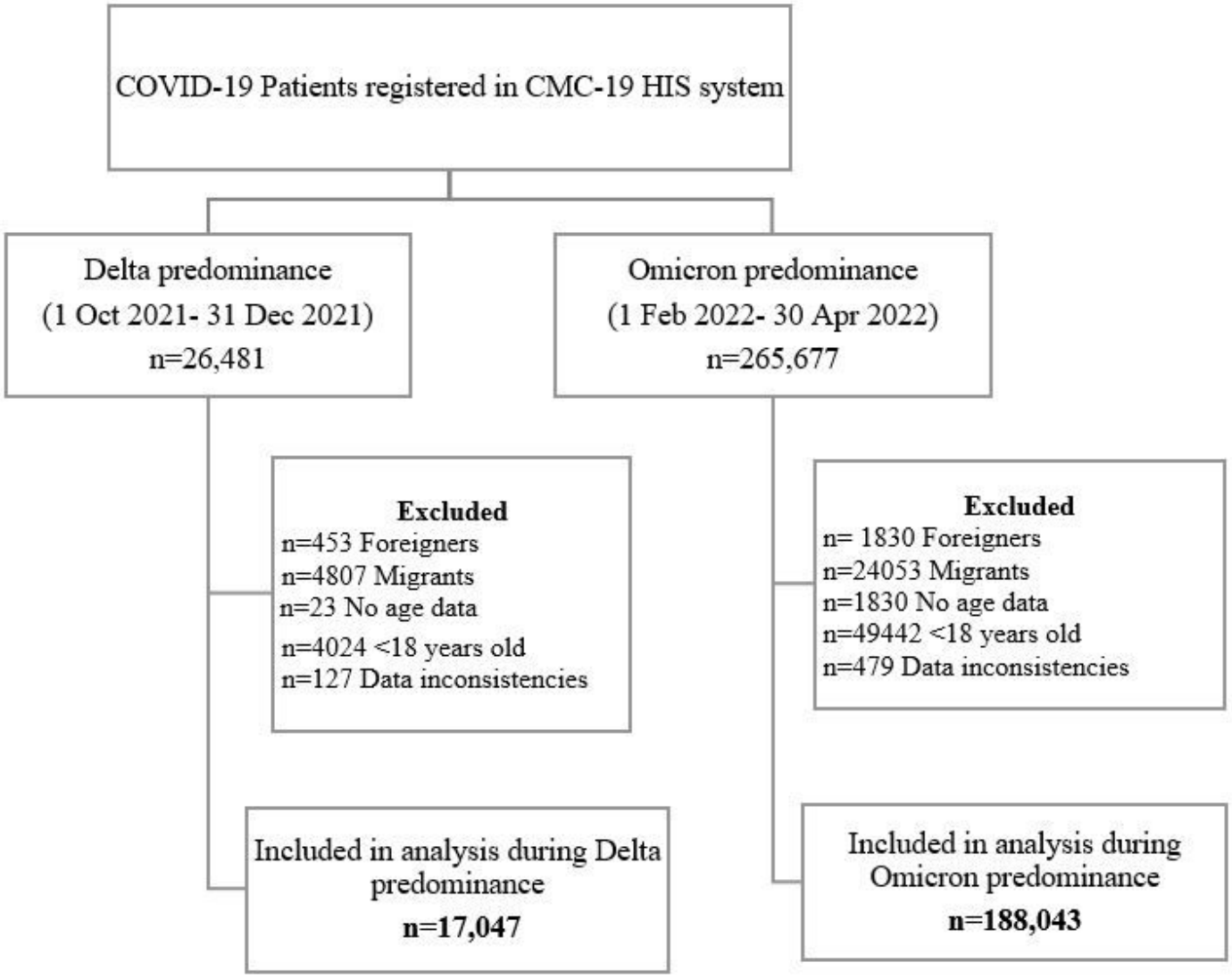
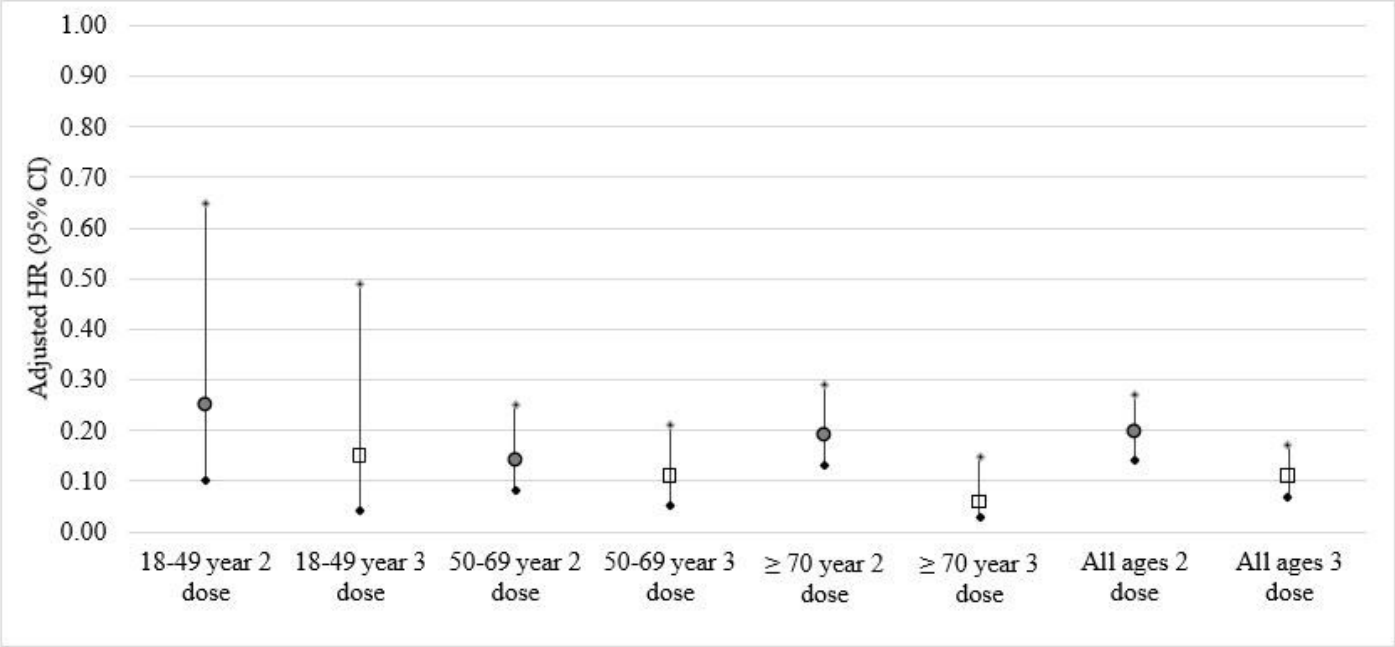


Figure 1

Flow chart of subject selection for adult COVID-19 patients who are residents of Chiang Mai, Thailand during Delta and Omicron predominance

Figure 2: Risk of severe COVID-19 among adult patients during omicron predominance, by two (●) and three (□) dose vaccination regimens stratified by age group

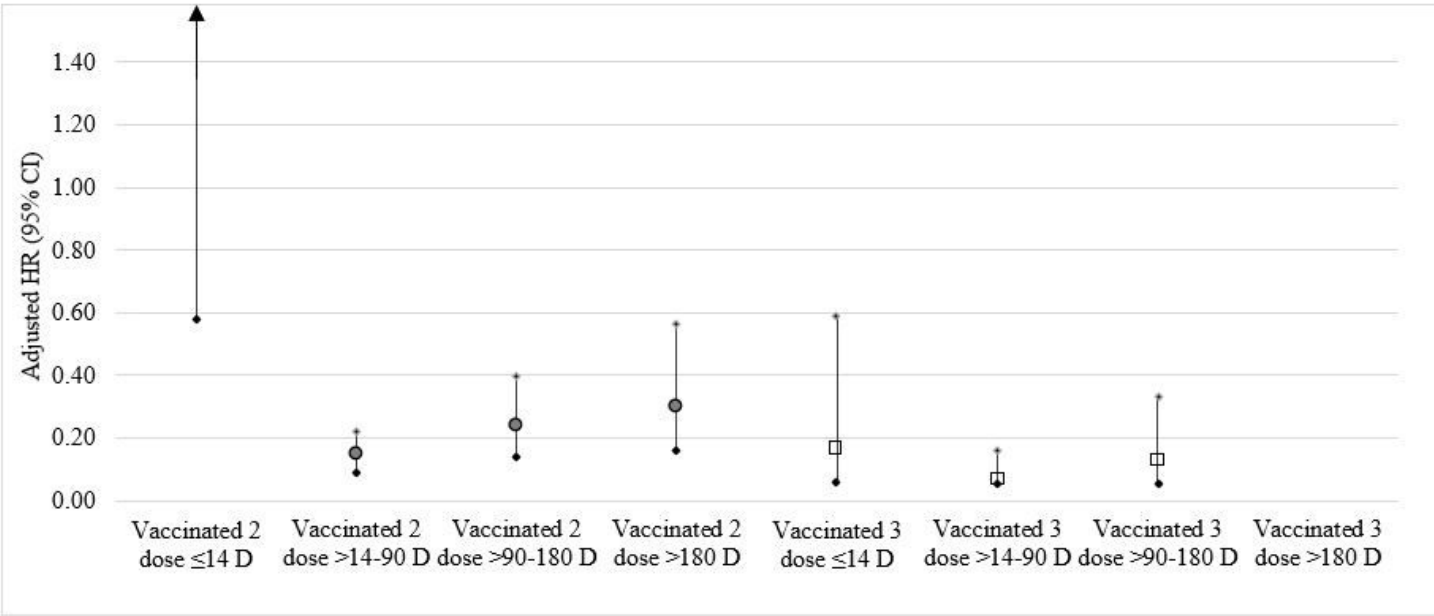


Adjusted for gender and calendar time. Reference group: Unvaccinated

Figure 2

See image above for figure legend.

Figure 3: Risk of severe COVID-19 among adult patients during omicron predominance, by two (●) and three (□) dose vaccination regimens stratified by time since last vaccine dose



Adjusted for age, gender and calendar time. Reference group: Unvaccinated

Figure 3

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20220827Supplementarymaterialforpreprintsubmission.pdf