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Reduction in severity and mortality in COVID-19 patients owing to heterologous third and fourth-dose vaccines during the periods of delta and omicron predominance in Thailand

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ABSTRACT

Objectives: The COVID-19 pandemic has evolved quickly, with different variants of concern resulting in the need for countries to offer booster vaccinations. Although studies have assessed homologous schedules in detail, the effectiveness of heterologous booster vaccine schedules against severity and mortality with newer variants remains to be explored fully.

Methods: Utilizing a 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 and omicron-predominant periods.

Results: Compared to omicron, COVID-19 cases during the delta period were 10 times more likely to have severe outcomes and in-hospital deaths. During omicron, a third vaccine dose had an 89% reduced risk of both severe COVID-19 and death. The third dose received 14-90 days before the date of the positive test showed the highest protection (93%). Severe outcomes were not observed with the third dose during delta, and the fourth dose during the omicron period. All the vaccine types used for boosting in Thailand offered similar protection against severe COVID-19.

Conclusion: Booster doses provided a very high level of protection against severe COVID-19 outcomes and deaths. Booster campaigns should focus on improving coverage by utilizing all available vaccines to ensure optimal protection.

Background

As of July 30, 2022, the COVID-19 pandemic caused by 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 (Mathieu *et al.*, 2022). This has unfortunately resulted in almost 6.4 million deaths worldwide, 1.5 million deaths across Asia, and over 31,000 deaths in Thailand (Mathieu *et al.*, 2022). 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 were responsible for reducing the clinical impact of COVID-19 substantially (Doroshenko, 2021; Moore *et al.*, 2021).

World Health Organization (2022) has licensed 11 COVID-19 vaccines to date, and globally almost 12 billion doses have been administered. There are six approved COVID-19 vaccines in Thai-

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land (Thailand Food and Drug Administration: Medicines Regulation Division, 2022) and a sustained effort by the government has resulted in 76% of the population being fully vaccinated and an additional 43% receiving three doses or above as of June 29, 2022 (Thailand department of disease control, 2022). The rollout of vaccinations in Thailand started with the inactivated vaccine (Sinovac) (Palacios *et al.*, 2021) in March 2021 followed by ChAdOx1 nCoV-19 (AstraZeneca) (Voysey *et al.*, 2021) in June 2021 and BNT162b2 (Pfizer-BioNTech) (Polack *et al.*, 2020) in October 2021. Owing to the 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. The fourth doses were administered widely beginning in January 2022, using BNT162b2, ChAdOx1 nCoV-19, and messenger RNA-1273 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 (Chuenkitmongkol *et al.*, 2022). Studies have reported higher neutralizing-antibody response with heterologous boosters as compared to homologous boosters (Atmar *et al.*, 2022; Barros-Martins *et al.*, 2021). However, there is limited data available on the protective benefit of heterologous schedules, particularly against newer variants of concern (Accorsi *et al.*, 2022; Liu *et al.*, 2021; Mayr *et al.*, 2022). The prevalent omicron variant is reported to have increased transmissibility, but lower clinical severity compared with the previous variants (Andrews *et al.*, 2022; Bager *et al.*, 2022; Nyberg *et al.*, 2022; Veneti *et al.*, 2022), and studies report reduced vaccine effectiveness against omicron infection (Andrews *et al.*, 2022; Nyberg *et al.*, 2022). Recent accounts of significant mortality due to omicron in elderly, under-vaccinated populations suggest omicron per se, may not be as mild as we think (Taiwan Centres for Disease Control, 2022; Taylor, 2022). Irrespective of variant type, 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 (Agrawal *et al.*, 2021; Whitaker *et al.*, 2022; Williamson *et al.*, 2020). It is important to understand how 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.

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

Methods

Study population

The current study draws on an a HIS network established in Chiang Mai, located in Northern Thailand, with a population of 1.6 million. Adult patients with confirmed COVID-19 infection 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 October 1, 2021-December 31, 2021 and February 1, 2022-April 30, 2022 periods, respectively. Patients with tests done in January 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 in Figure 1.

Data sources

We have previously published the details on creating and implementing the information systems used in this study (Intawong *et al.*, 2021). In brief, all COVID-19 cases detected in Chiang Mai province are reported into the HIS of Chiang Mai Provincial Health Office (CMC-19 HIS), under the Communicable Disease Control Act which mandates national reporting of all COVID-19 cases. CMC-19 HIS is a web-based reporting system launched in April 2021. 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 ID. The criteria for hospitalization were different during the delta and omicron periods. Even patients with mild infection who test positive for SARS-CoV-2 were admitted to hospital during delta period whereas asymptomatic or mild cases were treated as outpatient and isolated in designated places in community, or at home during the omicron period. Data on the 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 maintained by the Ministry of Public Health, Thailand.

Ethical approval statement

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.

Study design

We conducted a retrospective cohort study on Thai residents aged 18 years or older, with laboratory-confirmed SARS-CoV-2 infection during October 1-December 31, 2021 (Delta predominant) and February 1-April 30, 2022 (omicron predominant) time periods. The date of first positive SARS-CoV-2 test served as the index 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 and 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 nearly complete as the clinical information of all hospitalized COVID-19 cases of the 26 public and eight 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 SD or median and interquartile range

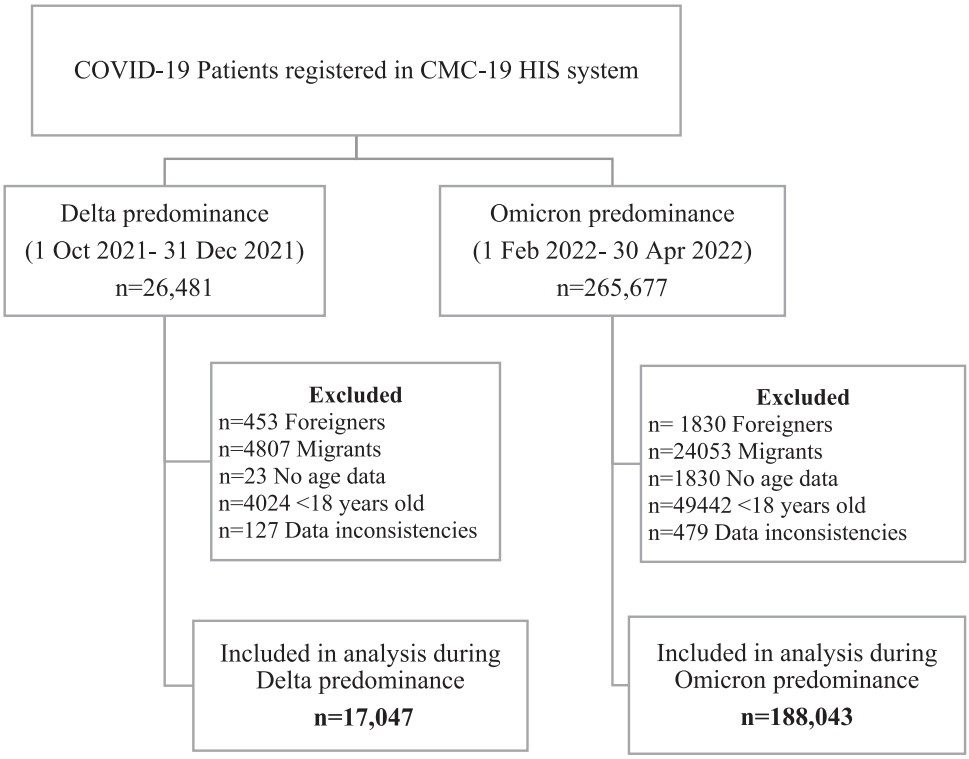

Figure 1. Flow chart of subject selection for adult COVID-19 patients who are residents of Chiang Mai, Thailand during Delta and Omicron predominance
CMC-19 HIS, Chiang Mai Provincial Health Office hospital information system.

(IQR) depending on the distribution. Categorical variables are summarized as frequency and percentages. Between-group comparisons were done using the Mann-Whitney-U test or *t*-test for continuous variables and the chi-square 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 hospitalized) or 30 days from the first positive SARS-CoV-2 test date (for non-hospitalized). 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 conducted using stata (version 15.0 SE, College station, TX:StataCorp LP). Significance tests are two 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 predominance, and 265,677 COVID-19 patients during the omicron predominance, 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 (Figure 1).

During delta predominance, a higher proportion of COVID-19 patients were male compared with 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).

Patients during delta predominance were more likely to have received ChAdOx1 nCoV-19 as the 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 rollout in Thailand. 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 (Table 2). 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).

During delta predominance, 77% of patients with severe outcomes were unvaccinated, compared with 37% without severe outcomes. During omicron predominance >50% of patients with severe outcomes were unvaccinated as compared with just 9% without severe outcomes. For both periods, patients who received at least one booster dose had very few events (Supplementary Figure 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 the date of positive test result (Table 2).

Among the COVID-19 patients who had received a third vaccine dose during delta predominance, 47%, 38% and 14% had received

Table 1
Comparison of clinical characteristics of COVID-19 patients during Delta predominance (October 1-December 31, 2021) with Omicron predominance (February 1-April 30, 2022) in Chiang Mai, Thailand

N = 205,090 Variable	Delta predominance	Omicron predominance	*P-value*
Number	**17,047**	**188,043**	-
Age, years			
Median (IQR)	38 (27-52)	38 (27-54)	*0.10*
Age group, n(%)			
18-29	5335 (31.3)	58,585 (31.2)	*<0.01*
30-39	3774 (22.1)	40,442 (21.5)	
40-49	3085 (18.1)	31,217 (16.6)	
50-59	2341 (13.7)	26,106 (13.9)	
60-69	1655 (9.7)	21,542 (11.5)	
≥70	857 (5.1)	10,151 (5.4)	
Gender, n(%)			
Female	8742 (51.3)	103,852 (55.2)	*<0.01*
Male	8305 (48.7)	84,191 (44.8)	
COVID-19 outcomes			
Severe COVID-19, n(%)	192 (1.13)	195 (0.10)	*<0.01*
Invasive mechanical ventilation, n(%)	130 (0.76)	117 (0.06)	*<0.01*
Median (IQR) time from first positive test to nvasive mechanical ventilation, 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)	16,372 (8.7)	*<0.01*
Vaccinated one dose	3374 (19.8)	2968 (1.6)	
Vaccinated two doses	6843 (40.1)	96,382 (51.3)	
Vaccinated three doses	492 (2.9)	65,492 (34.8)	
Vaccinated four doses	0 (0)	6829 (3.6)	
Type of primary vaccine series, n(%)	**n = 6843**	**n = 96,382**	
Sinovac/ Sinopharm-ChAdOx1	3071 (44.9)	39,553 (41.0)	*<0.01*
Sinovac- Sinovac or SP-SP	2840 (41.5)	13,522 (14.0)	
ChAdOx1- ChAdOx1	650 (9.5)	2845 (2.9)	
Pfizer- Pfizer	87 (1.3)	10,615 (11.0)	
ChAdOx1- Pfizer/Moderna	178 (2.6)	25,711 (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 = 65,492**	
Pfizer-BioNTech	187 (38.0)	31,589 (48.2)	*<0.01*
ChAdOx1 (AstraZeneca)	231 (47.0)	20,313 (31.0)	
Moderna	68 (13.8)	13,531 (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 = 10,709**	**n = 171,671**	
≤14 days	2979 (27.8)	6289 (3.7)	
>14-90 days	6520 (60.9)	76,696 (44.7)	
>90-180 days	1183 (11.1)	80,013 (46.6)	
>180 days	27 (0.2)	8673 (5.0)	

IQR, interquartile range

ChAdOx1 nCoV-19, 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 nCoV-19, Pfizer-BioNTech, and Moderna, respectively (Chariyalertsak *et al.*, 2022). Severe outcomes were not observed in those who received a third dose.

The vaccine types used for the 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 nCoV-19, 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 nCoV-19, Pfizer-BioNTech, and Moderna, respectively (Chariyalertsak *et al.*, 2022). Severe outcomes were not observed in those who received a fourth dose.

Factors associated with severe COVID-19 outcomes and mortality

During both delta and omicron predominance older age and male gender were associated with a 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 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 the test, receiving the primary vaccination series was associated with 87% and 89% reduction of risk of severe COVID-19 and mortality, respectively compared with 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 mortal-

Table 2
Comparison of clinical characteristics of COVID-19 patients with and without severe outcomes during Delta predominance (October 1- December 31, 2021) and Omicron predominance (February 1- April 30, 2022) in Chiang Mai, Thailand

	Delta predominance (N = 17,047)			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)	16,855 (98.87)	-	195 (0.1)	187,848 (99.9)	
Age, years						
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)	58,577 (31.2)	*<0.01*
30-39	6 (3.1)	3768 (22.4)		7 (3.6)	40,435 (21.5)	
40-49	13 (6.8)	3072 (18.2)		11 (5.6)	31,206 (16.6)	
50-59	35 (18.2)	2306 (13.7)		26 (13.3)	26,080 (13.8)	
60-69	51 (26.6)	1604 (9.5)		39 (20.0)	21,503 (11.4)	
≥70	85 (44.3)	772 (4.6)		104 (53.4)	10,047 (5.4)	
Gender, n(%)						
Male	104 (54.2)	8201 (48.7)	*<0.01*	120 (61.5)	84,071 (44.8)	*<0.01*
Female	88 (45.8)	8654 (51.3)		75 (38.5)	103,777 (55.2)	
Vaccination status, n(%)						
Unvaccinated	148 (77.1)	6190 (36.7)	*<0.01*	103 (52.8)	16,269 (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)	96,320 (51.3)	
Vaccinated three doses	0 (0)	492 (2.9)		24 (12.3)	65,468 (34.9)	
Vaccinated four doses				0 (0)	6829 (3.6)	
Type of primary vaccine series, n(%)	**n = 16**	**n = 6827**		**n = 62**	**n = 96,320**	
Sinovac/ Sinopharm-ChAdOx1	8 (50.0)	3063 (44.9)	-	14 (22.6)	39,539 (41.1)	*0.010*
Sinovac- Sinovac or SP-SP	3 (18.8)	2837 (41.6)		8 (12.9)	13,514 (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)	10,608 (11.0)	
ChAdOx1- Pfizer/Moderna	1 (6.2)	177 (2.6)		24 (38.7)	25,687 (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 = 65,468**	
Pfizer-BioNTech		187 (38.1)	-	12 (50.0)	31,577 (48.2)	*0.967*
ChAdOx1 (AstraZeneca)		231 (46.9)		8 (33.3)	20,305 (31.0)	
Moderna		68 (13.8)		4 (16.7)	13,527 (20.7)	
Other		6 (1.2)		0 (0)	59 (0.1)	
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 = 10,665**		**n = 92**	**n = 171,579**	
≤14 days	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)	76,659 (44.7)	
>90-180 days	2 (4.6)	1181 (11.1)		36 (39.1)	79,977 (46.6)	
>180 days	0 (0)	27 (0.2)		12 (13.0)	8661 (5.0)	

IQR, interquartile range

ity (Supplementary Figure 2 and Supplementary Table 1a). Risk reduction against severe COVID-19 outcomes was 88% among those who received the primary series 14-90 days prior to the date of positive SARS-CoV-2 test as compared to 72% for those vaccinated ≤14 days. 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 >90-180 days (Supplementary Table 1a). Limited sample size prevents drawing inferences for one vaccine dose >180 days and two doses >90 days.

During omicron predominance, severe outcomes 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 0.07-0.17) and mortality (HR 0.11, 95% CI 0.06-0.21), compared with 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 (Figure 2). All three vaccine types used for boosting, ChAdOx1 nCoV-19, Pfizer-BioNTech, and Moderna, offered similar protection against severe COVID-19 (Supplementary Figure 3).

Patients who received the third dose 14-90 days before the date of positive SARS-CoV-2 test had a risk reduction of 93% against severe COVID-19 outcomes followed by 87% among those vaccinated >90 days and 83% among those vaccinated ≤14 days. Similarly, those who received the primary series 14-90 days had the highest risk reduction (85%), and waning was observed >90days (76%) and >180 days (70%). Receiving the primary series ≤14 days was not

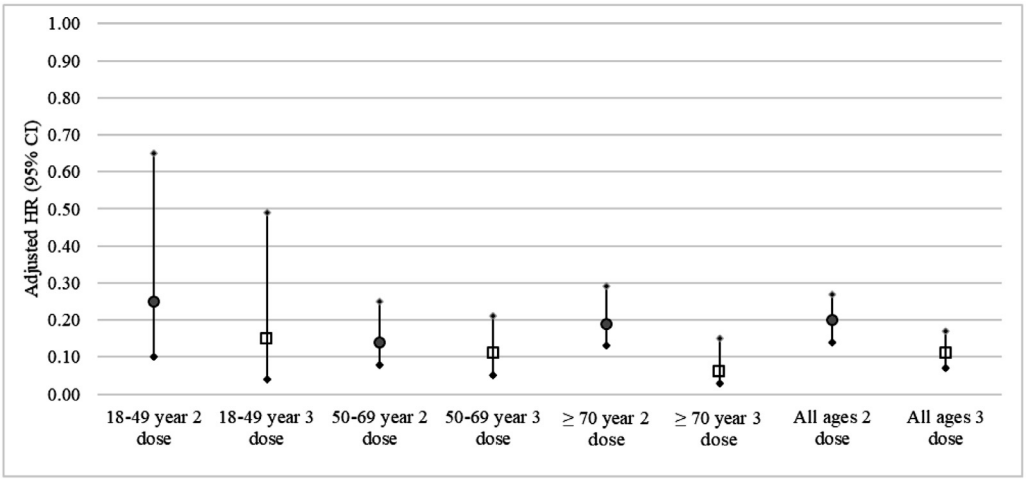

Figure 2. Risk of severe COVID-19 among adult patients during omicron predominance, by two (•) and three (•) dose vaccination regimens stratified by age group
Adjusted for gender and calendar time. Reference group: Unvaccinated HR, hazard ratio.

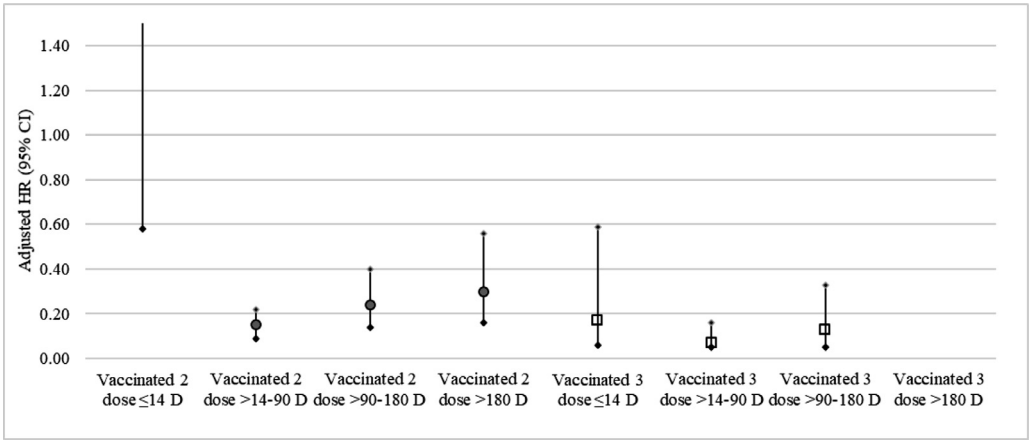

Figure 3. Risk of severe COVID-19 among adult patients during omicron predominance, by two (•) and three (•) dose vaccination regimens stratified by time since last vaccine dose
Adjusted for age, gender and calendar time. Reference group: Unvaccinated HR, hazard ratio.

protective against severe outcomes during omicron predominance (Supplementary Table 1b, Figure 3). Limited sample size prevents drawing inferences for three vaccine doses >180 days.

Discussion

Although 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 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 compared with the delta variant (Andrews *et al.*, 2022; Divino *et al.*, 2022; Nyberg *et al.*, 2022; Veneti *et al.*, 2022). We observed 10 times lower rate of mortality and IMV use, which is consistent with values previously reported. However, it should be noted that before 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, UK, and Denmark (Bager *et al.*, 2022; Nyberg *et al.*, 2022; Veneti *et al.*, 2022). 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, the authors wish to highlight that the sample size of three dose recipients during delta predominance (n = 492) maybe underpowered to detect severe outcomes. Protective role of vaccines is confirmed with our findings. 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.

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 received 14-90 days from the last vaccine dose. The risk reduction dropped by nine and fifteen percentage points at >90 days and >180 days respectively for two dose regime and by six percentage points 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 US-CDC study 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 (Ferdinands *et al.*, 2022). Similar findings were reported in a study among long-term care residents in Sweden (Nordström *et al.*, 2022) and more recently from Malaysia (Suah *et al.*, 2022), where protection was observed to wane from 3rd month onwards.

Our study found that the three vaccine types used for boosting in Thailand, ChAdOx1 nCoV-19, Pfizer-BioNTech and Moderna, offered similar protection against severe COVID-19 outcomes. Comparable protection from ChAdOx1 nCoV-19 and Pfizer-BioNTech against infection, hospitalization, intensive care unit admissions and deaths, has been previously reported (Bhatnagar *et al.*, 2022; Chuenkitmongkol *et al.*, 2022; Nyberg *et al.*, 2022). Our findings corroborate this evidence and strongly supports the use of ChAdOx1 nCoV-19, Pfizer-BioNTech and Moderna as booster vaccines, providing much needed flexibility to incorporate different vaccines into schedules according to local supply and logistical considerations.

Our data strongly suggests that accelerating the third and fourth-dose vaccinations and increasing coverage by using any vaccines available, particularly among elderly is an important strategy to optimize protection. The authors wish to highlight a few study limitations. 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. The source population were those diagnosed with COVID-19, and the testing could have been done for reasons other than signs and symptoms or clinical suspicion. We did not differentiate or control for incidental finding of COVID-19.

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 after the fourth dose is 75 days with a median of 53 days. 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.

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Author contributions

All authors contributed to the conception and design of the study, SC, KC, TW, WK, PA, NC, KN, WT, KK, PP and PK were responsible for acquisition of data, KI, SC and AT were responsible for the analysis and interpretation of data, all authors contributed to drafting the article and revising it critically. All authors approved the final version of the manuscript submitted.

Declaration of competing interest

The authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.11.006.

References

Accorsi EK, Britton A, Shang N, et al. Effectiveness of homologous and heterologous Covid-19 boosters against omicron. N Engl J Med 2022;386:2433–5.
Agrawal U, Katikireddi SV, McCowan C, 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. Lancet Respir Med 2021;9:1439–49.
Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022;386:1532–46.
Atmar RL, Lyke KE, Deming ME, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med 2022;386:1046–57.
Bager P, Wohlfahrt J, Bhatt S, et al. Risk of hospitalisation associated with infection with SARS-CoV-2 omicron variant versus delta variant in Denmark: an observational cohort study. Lancet Infect Dis 2022;22:967–76.
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;27:1525–9.
Bhatnagar T, Chaudhuri S, Ponnaiah M, et al. Effectiveness of BBV152/Covaxin and AZD1222/Covishield vaccines against severe COVID-19 and B.1.617.2/Delta variant in India, 2021: a multi-centric hospital-based case-control study. Int J Infect Dis 2022;122:693–702.
Chariyalertsak S, Intawong K, Chalom K, et al. Effectiveness of heterologous 3rd and 4th dose COVID-19 vaccine schedules for SARS-CoV-2 infection during delta and omicron predominance in Thailand. Research Square 2022 https://www.researchsquare.com/article/rs-1792139/v1. [Accessed 28 June 2022].
Chuenkitmongkol S, Solante R, Burhan E, et al. Expert review on global real-world vaccine effectiveness against SARS-CoV-2. Expert Rev Vaccines 2022;21:1255–68.
Divino F, Alaimo Di Loro P, Farcomeni A, et al. Decreased severity of the Omicron variant of concern: further evidence from Italy. Int J Infect Dis 2022;119:21–3.
Doroshenko A. The combined effect of vaccination and nonpharmaceutical public health interventions-ending the COVID-19 pandemic. JAMA Netw Open 2021;4.
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;71:255–63.
Intawong K, Olson D, Chariyalertsak S. Application technology to fight the COVID-19 pandemic: lessons learned in Thailand. Biochem Biophys Res Commun 2021;538:231–7.
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;398:856–69.
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;386:1375–7.
Moore S, Hill EM, Tildesley MJ, Dyson L, Keeling MJ, et al. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. Lancet Infect Dis 2021;21:793–802.
Nordström P, Ballin M, Nordström A. 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. Lancet Reg Health Eur 2022;21.
Nyberg T, 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 2022;399:1303–12.
Palacios R, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV study. SSRN Journal 2021 https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3822780.
Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603–15.
Suah JL, Husin M, Tok PSK, et al. Waning COVID-19 vaccine effectiveness for BNT162b2 and CoronaVac in Malaysia: an observational study. Int J Infect Dis 2022;119:69–76.
Mathieu E, Ritchie H, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). https://ourworldindata.org/coronavirus, 2022 (accessed 31 July, 2022).
Taiwan Centres for Disease Control. COVID-19 Dashboard. https://www.cdc.gov.tw/En, 2022 (accessed 08 Aug 2022).
Taylor L. Covid-19: Hong Kong reports world's highest death rate as zero covid strategy fails. BMJ 2022;376:o707.
Thailand department of disease control, 2022, https://ddc.moph.go.th/dcd/pagecontent.php?page=994&dept=dcd (accessed 21 July, 2022).
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. Euro Surveill 2022;27.
Voysey M, Clemens SAC, 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 Correction appears in: 2021;397:98.
Whitaker HJ, Tsang RSM, Byford R, et al. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response amongst individuals in clinical risk groups. J Infect 2022;84:675–83.
Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.