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Original Article

Heterologous booster vaccines reduce severity and mortality in COVID-19 during BA.2 and BA.4/BA.5 omicron predominance in Thailand

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Abstract *Background:* The COVID-19 pandemic has evolved quickly, with variants of concern resulting in the need to offer booster vaccinations. Unfortunately, the booster uptake has been slow and vaccine response has shown to wane over time. Therefore, it's critical to evaluate the role of vaccinations on outcomes with newer sub-lineages of omicron.
Methods: Utilising a Hospital Information System established in Chiang Mai, Thailand, we conducted a cohort study by linking patient-level data of laboratory-confirmed COVID-19 cases to the national immunization records, during BA.2 and BA.4/BA.5 predominance.
Results: In adjusted cox-proportional hazard models, BA.4/BA.5 was not associated with more severe COVID-19 outcomes or deaths as compared to BA.2. Risk of severe outcomes and deaths were significantly reduced with third (87% and 95%) and fourth (88% and 95%) dose vaccination,

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while events were not observed with a fifth dose. Across the regimens, vaccination within 14—90 days prior showed the highest level of protection. All the vaccine types used for boosting in Thailand offered similar protection against severe COVID-19.

Conclusions: Boosters provide high level of protection against severe COVID-19 outcomes and deaths with newer omicron sub-lineages. Booster campaigns should focus on improving coverage utilising all available vaccines to ensure optimal protection.

Introduction

As of 1 December 2022, the Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 650 million confirmed cases and 6.7 million deaths globally, with almost 5 million cases and 33,000 deaths in Thailand alone.[1] The omicron variant of SARS-CoV-2, first described in November 2021, has spread rapidly to become globally dominant.[2] Over time, several omicron sub-lineages have emerged and at the time of analysis, the BA.4/BA.5 sub-lineages dominated in most regions of Thailand.[2]

The rapid development and deployment of vaccines has significantly reduced the clinical impact of COVID-19.[3] There are seven COVID-19 vaccines currently approved in Thailand[4] and a sustained effort by the government has resulted in 77.6% of the population being fully vaccinated and an additional 38.5%% receiving three doses and 9.4% receiving four doses or more as of 2 December 2022.[5] The primary series vaccinations in Thailand started with inactivated vaccines (Sinovac)[6] in March 2021 followed by ChAdOx1 nCoV-19 (AstraZeneca)[7] in June 2021 and BNT162b2 (Pfizer-BioNTech)[8] in October 2021. Due to challenges in vaccine supply and to manage public concerns around the effectiveness of the inactivated vaccine, heterologous schedules were implemented since July 2021. The fourth dose (second booster) vaccines were widely administered from January 2022 onwards using BNT162b2, ChAdOx1 nCoV-19 and mRNA-1273.

While vaccines have been able to successfully control infection with ancestral strains of SARS-CoV-2, studies report reduced vaccine effectiveness against newer variants, particularly infection with omicron variant.[9,10] Of particular concern are BA.4/BA.5 sub-lineages which display evasion of neutralizing antibodies, when compared with ancestral strains[11] and against plasma from triple-vaccinated individuals and from those who developed a BA.1 infection after vaccination.[12] This immune escape combined with the waning of immune response to COVID-19 vaccination may have contributed to the recent waves with BA.4/BA.5 infection in many countries.[13] Very few studies have examined the severity of clinical outcomes with BA.4/BA.5 sub-lineages.[14]

The initial clinical trials evaluated vaccine 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.[15] Studies have reported higher neutralizing-antibody response with heterologous boosters as compared to homologous boosters.[16,17] However, there is limited data available on the protective benefit of heterologous schedules against more recent variants of concern.[18,19] Similar to Thailand, most countries in Asia implemented heterologous vaccination schedules widely and early in the pandemic.

We have previously evaluated the role of heterologous vaccination schedules on infection rates[20] and severe COVID-19 outcomes[21] during delta and early omicron predominant periods in Thailand. Now that uptake of booster vaccinations have plateaued and it is clear that vaccine response wanes with time, for this paper, we have conducted a more recent evaluation of the impact COVID-19 vaccinations have on clinical outcomes with newer sub-lineages of omicron, particularly BA.4/BA.5. As COVID-19 infections have tended to be milder with more recent variants, we have focused on severe clinical outcomes, aiming to evaluate vaccination factors contributing to poorer outcomes.

Methods

Study population

The current study draws on a unique hospital information system (HIS) established in Chiang Mai, located in Northern Thailand, with a population of 1.6 million. Adults with laboratory confirmed COVID-19 between 1 May — 31 July 2022 were included in the study. To understand the circulating SARS-CoV-2 variant, the ministry of health performs molecular testing on a random sample of COVID-19 positive cases every month. Results from northern Thailand revealed that BA.2 omicron sub-lineage accounted for >99% of the cases in May, with BA.4/BA.5 appearing from mid-June onwards. Subsequently, BA.4/BA.5 spread rapidly, dominating through July to >90% of cases by mid-August. We used this molecular evidence as guidance to differentiate the period from 1 May — 30 June as BA.2 predominant and 1 July onwards as BA.4/BA.5 predominant. A similar methodology was followed in our previous studies to differentiate the periods by variant predominance.[20,21]

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

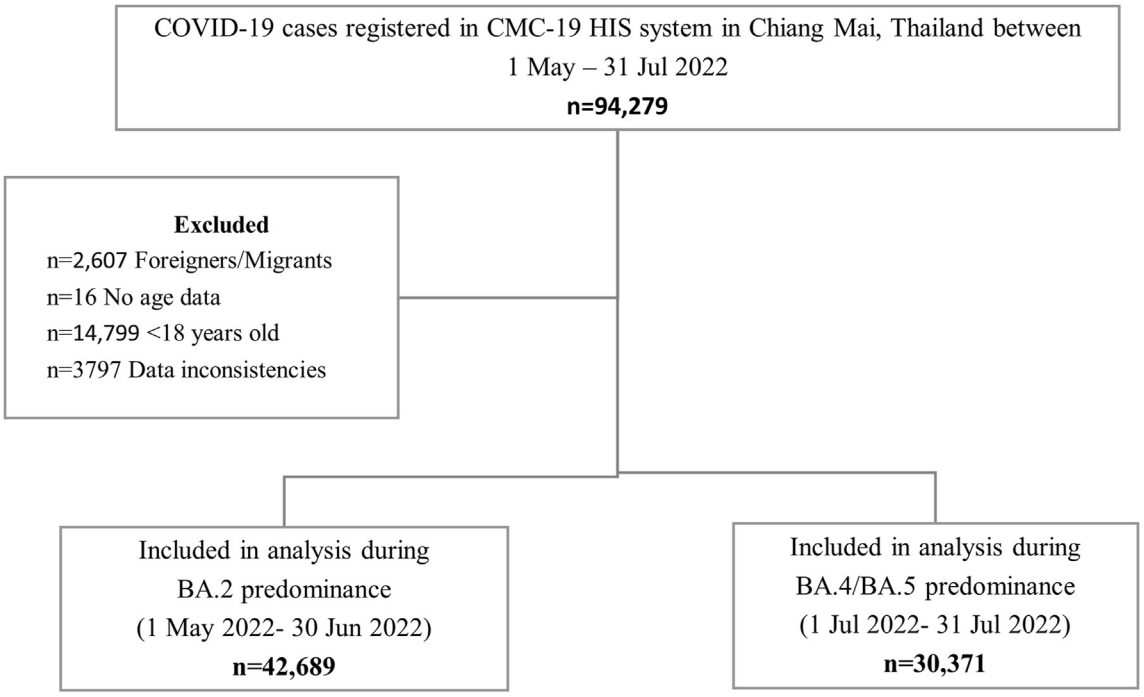

Figure 1. Flow chart of subject selection for adult COVID-19 cases who are residents of Chiang Mai, Thailand between 1 May – 31 July 2022.

Data sources

We have previously published the details on creating and implementing the information systems used in this study.[22] In brief, all COVID-19 cases detected in Chiang Mai province are reported into the web based HIS of Chiang Mai Provincial Health Office (CMC-19 HIS). Reporting of all COVID-19 cases is mandatory under the Communicable Disease Control Act. When a COVID-19 case is detected, either at screening centers, hospitals or outpatient clinics, the healthcare staff enter the patient details, including laboratory results into the CMC-19 HIS under a unique ID. Data on severity and progression of the disease including requirement of ventilatory support and treatments are recorded in each hospital's information system, which is linked with CMC-19 HIS. Deaths which occur within the province are reported to Chiang Mai Provincial Health Office and are routinely updated in CMC-19 HIS.

All national vaccination records are centrally captured in 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 within routine public health surveillance protocols in Chiang Mai and all data was collected as part of the national COVID-19 response under the Communicable Disease ACT (B.E. 2558) with waiver of informed consent by institutional review boards in Chiang Mai province.

Study design

We conducted a retrospective cohort study on Thai residents aged 18 years or older, with a laboratory confirmed SARS-CoV-2 infection during 1 May – 31 July 2022 period. Date of first positive SARS-CoV-2 test served as the index date. Reinfections, defined as a positive SARS-CoV-2 test at least 90 days prior, accounted for <0.6% of this cohort.

Baseline clinical characteristics and SARS-CoV-2 test details were extracted from the CMC-19 HIS. 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 and/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 providing IMV support 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 the predominant omicron sub-lineage (BA.2 or BA.4/BA.5), to understand how the clinical characteristics and other risk factors differed between the periods. Continuous variables are summarized as mean and standard deviation (SD) for

normally distributed data or median and interquartile range (IQR) for skewed data. 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, as appropriate.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) for severe COVID-19 and mortality outcomes. Follow up period was taken from the first positive SARS-CoV-2 test date and censored at the earliest of: date of first starting IMV, date of death, or 30 days from first positive SARS-CoV-2 test date, whichever was earliest. 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), omicron sublineage (BA.2 or BA.4/BA.5), 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. For simplicity, we opted to show the percentage risk reduction as this is more easily interpreted by the vaccine community. We calculated risk reduction (RR) from HRs as RR = (1-HR) x 100%.

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 55,383 COVID-19 cases during BA.2 predominance, and 38,896 COVID-19 cases during BA.4/BA.5 predominance, in Chiang Mai province. After applying the exclusion criteria, 42,689 and 30,371 Thai residents above 18 years of age were included in the final analysis for the BA.2 and BA.4/BA.5 predominant periods respectively (Fig. 1).

Subjects in BA.4/BA.5 predominance were more likely to be younger as compared to BA.2 period. No significant difference in gender distribution was observed between the two periods. Occurrence of severe COVID-19 outcomes were similar in both BA.2 and BA.4/BA.5 predominance. However, cases during BA.2 period had twice the mortality rate as compared to BA.4/BA.5 period (0.12% vs 0.06%, $p=0.018$) (Table 1).

The distribution of doses received by subjects in BA.4/BA.5 predominance indicated slightly higher proportions of unvaccinated individuals (14.7% vs 10.7% during BA.2) whilst also showing slightly higher uptake of fourth and fifth doses by subjects during BA.4/BA.5 predominance (Table 1). Over 50% of the subjects in both periods had at least one booster vaccine. During both BA.2 and BA.4/BA.5 periods the proportion of subjects receiving Moderna increased progressively across third (22.9% and 26.1%), fourth (52.4% and 57.2%) and fifth (87.3% and 83.8%) doses respectively, which is reflective of the booster dose roll-out in Thailand. The heterogeneous nature of the vaccination programme in Thailand is reflected in the observed uptake in this study: Approx 33% of primary schedules were a mix

Table 1 Comparison of clinical characteristics of adult COVID-19 cases during BA.2 predominance with BA.4/BA.5 predominance in Chiang Mai, Thailand.

N = 73,060 Variable	BA.2 predominance	BA.4/BA.5 predominance	*p-value*
Number	42,689	30,371	-
Age, years			
Median (IQR)	41 (29–58)	39 (28–56)	*<0.01*
Age group, n (%)			
18–29	11251 (26.4)	8992 (29.6)	*<0.01*
30–39	8944 (20.9)	6682 (22.0)	
40–49	6855 (16.1)	4617 (15.2)	
50–59	6183 (14.5)	3792 (12.5)	
60–69	5990 (14.0)	3899 (12.8)	
≥70	3466 (8.1)	2389 (7.9)	
Gender, n (%)			
Female	24644 (57.7)	17366 (57.2)	*0.139*
Male	18045 (42.3)	13005 (42.8)	
Clinical outcomes			
Severe COVID-19, n (%)	87 (0.20)	51 (0.17)	*0.270*
Invasive Mechanical Ventilation, n (%)	50 (0.12)	37 (0.12)	*0.850*
Median (IQR) time from first positive test to IMV, days	1 (1–2)	1 (1–3)	*0.960*
Deaths, n (%)	50 (0.12)	19 (0.06)	*0.018*
Median (IQR) time from first positive test to death, days	5 (2–10)	3 (2–6)	*0.110*
Vaccination Status, n (%)			
Unvaccinated	4581 (10.7)	4469 (14.7)	*<0.01*
Vaccinated One dose	494 (1.1)	240 (0.8)	
Vaccinated two doses	14261 (33.4)	8139 (26.8)	
Vaccinated three doses	18799 (44.0)	13177 (43.4)	
Vaccinated four doses	4444 (10.4)	4062 (13.4)	
Vaccinated five doses	110 (0.3)	284 (0.9)	
Type of primary vaccine series, n (%)	**n=14,261**	**n=8,139**	
Sinovac/ Sinopharm-ChAdOx1 nCoV-19	4787 (33.6)	2697 (33.1)	*<0.01*
Sinovac–Sinovac or Sinopharm –Sinopharm	1812 (12.7)	1203 (14.8)	
ChAdOx1 nCoV-19-ChAdOx1 nCoV-19	451 (3.2)	306 (3.8)	

(*continued on next page*)

Table 1 (*continued*)

N = 73,060 Variable	BA.2 predominance	BA.4/BA.5 predominance	*p-value*
Pfizer-BioNTech-Pfizer-BioNTech	1960 (13.7)	1292 (15.8)	
ChAdOx1 nCoV-19-Pfizer-BioNTech/Moderna	4328 (30.3)	2096 (25.8)	
Sinovac/Sinopharm-Pfizer-BioNTech/Moderna	74 (0.5)	56 (0.7)	
Moderna–Moderna	849 (5.9)	489 (6.0)	
Type of third vaccine dose, n (%)	**n = 18,799**	**n = 13,177**	
Pfizer-BioNTech	9965 (53.0)	6932 (52.6)	*<0.01*
ChAdOx1 nCoV-19	4522 (24.0)	2792 (21.2)	
Moderna	4299 (22.9)	3441 (26.1)	
Other	13 (0.1)	12 (0.1)	
Type of fourth vaccine dose[a], n (%)	**n = 4,443***	**n = 4,062**	
Pfizer-BioNTech	1953 (43.9)	1609 (39.6)	*<0.01*
ChAdOx1 nCoV-19	163 (3.7)	129 (3.2)	
Moderna	2326 (52.4)	2322 (57.2)	
Other	1 (0.02)	2 (0.05)	
Type of fifth vaccine dose, n (%)	**n = 110**	**n = 284**	
Pfizer-BioNTech	14 (12.7)	46 (16.2)	*0.390*
Moderna	96 (87.3)	238 (83.8)	
Median (IQR) time since last vaccination, days	138 (101–176)	180 (128–217)	*<0.01*
Time since last vaccination, n (%)			
≤14days	696 (1.9)	462 (1.9)	*<0.01*
>14–90 days	6926 (19.1)	3219 (12.9)	
>90–180 days	20366 (56.0)	8944 (35.8)	
>180 days	8352 (23.0)	12342 (49.4)	

[a] Vaccine type missing in 1 subject.
IMV = Invasive Mechanical Ventilation, IQR = Interquartile range.

of Sinovac/Sinopharm-ChAdOx1 nCoV-19 vaccines with another 25–30% taking ChAdOx1 nCoV-19-Pfizer-BioNTech/Moderna vaccines (Table 1). Similarly, just over 50% of third doses were Pfizer-BioNTech while more than 50% of fourth doses and over 80% of fifth doses were Moderna vaccines. Half of the subjects who tested positive in BA.4/BA.5 predominance received their last vaccine >180 days ago, as compared just under a quarter of subjects who tested positive in BA.2 predominance (Table 1).

Severe COVID-19 outcomes

Severe COVID-19 outcomes and deaths were observed in 87 (0.20%) and 50 (0.12%) cases during BA.2 predominance and 51 (0.17%) and 19 (0.06%) cases during BA.4/BA.5 predominance, respectively. Subjects with severe COVID-19 outcomes during BA.2 predominance were nearly 30 years older as compared those without severe outcomes, while for BA.4/BA.5 predominance this age gap increased to 35 years. >70% of patients with severe outcomes were aged 60 years or older during both periods (Table 2). No significant difference between genders were observed.

Over 50% of the subjects with severe outcomes during both BA.2 and BA.4/BA.5 predominance were not fully vaccinated, as compared to ~15% among those without severe outcomes. For both periods, patients who have received booster doses had very few events. Among the vaccinated, there was no significant difference in time since last vaccination between those with and without severe outcomes in BA.2 period. However, during BA.4/BA.5 predominance, subjects with severe outcomes had a significantly longer time lapse from date of last vaccination as compared to those without severe outcomes (median 237 vs 180 days, $p < 0.001$) (Table 2).

Factors associated with severe COVID-19 outcomes and mortality

In adjusted models, BA.4/BA.5 was not associated with more severe outcomes or deaths as compared to BA.2. After adjusting for gender, calendar time of test, type of omicron sub-lineage and number of vaccines received, older age was significantly associated with higher risk of both severe COVID-19 and mortality. This indicates that despite vaccination, older age groups remain vulnerable to severe COVID-19 and deaths warranting additional protective measures in this group (Supplementary Table 1).

Severe outcomes or deaths were not observed among fifth dose recipients after a median follow up of 48 (IQR 12–93) days from last vaccination. After adjusting for age, gender, calendar time of test and type of sub-lineage, receiving a third and fourth dose was associated with 87% (95% CI 78 to 93%) and 88% (95% CI 72 to 95%) reduced risk of severe COVID-19, respectively. Both third (95%, 95% CI 84 to 98%) and fourth (95%, 95% CI 76 to 99%) dose vaccination was associated with very high reductions of risk of mortality, as compared to the unvaccinated group. Receiving only the primary series had moderate reductions of risk of severe outcomes (57%, 95% CI 35 to 71%) and deaths (61%, 95% CI 32 to 78%) (Supplementary Table 1).

In age stratified adjusted models, subjects aged 60 years or older had consistently lower risk reduction with two and three doses of the vaccine as compared to those younger than 60 years. Severe outcomes were not observed among fourth dose recipients aged ≥60 years, and fifth dose recipients in both age groups (Fig. 2, Supplementary Table 1).

Across the vaccine regimens, those who received the vaccination within 14–90 days prior to the date of positive SARS-CoV-2 test appear to have highest level of protection against severe outcomes. After adjusting for age, gender, calendar time of test and type of omicron sub-lineage,

Table 2 Comparison of clinical characteristics of adult COVID-19 cases with and without severe outcomes during BA.2 and BA.4/BA.5 predominance in Chiang Mai, Thailand.

Variable	BA.2 predominance (N = 42,689)			BA.4/BA.5 predominance (N = 30,371)		
	Without severe COVID-19 outcome	With severe COVID-19 outcome	*p-value*	Without severe COVID-19 outcome	With severe COVID-19 outcome	*p-value*
Number (%)	42602 (99.8)	87 (0.2)	–	30320 (99.8)	51 (0.2)	–
Age, years						
Median (IQR)	41 (29–58)	70 (55–82)	*<0.01*	39 (28–56)	74 (59–86)	*<0.01*
Age group, n (%)						
18–29	11249 (26.4)	2 (2.3)	*<0.01*	8991 (29.7)	1 (1.9)	*<0.01*
30–39	8937 (20.9)	7 (8.0)		6682 (22.0)	0 (0)	
40–49	6851 (16.1)	4 (4.6)		4612 (15.2)	5 (9.8)	
50–59	6172 (14.5)	11 (12.6)		3785 (12.5)	7 (13.7)	
60–69	5971 (14.0)	19 (21.8)		38894 (12.8)	5 (9.8)	
≥70	3422 (8.0)	44 (50.6)		2356 (7.8)	33 (64.7)	
Gender, n (%)						
Male	18002 (42.3)	43 (49.4)	*0.176*	12980 (42.8)	25 (49.0)	*0.370*
Female	24600 (57.7)	44 (50.6)		17340 (57.2)	26 (51.0)	
Vaccination Status, n (%)						
Unvaccinated	4542 (10.7)	39 (44.8)	*<0.01*	4439 (14.6)	30 (58.8)	*<0.01*
Vaccinated One dose	491 (1.1)	3 (3.5)		239 (0.8)	1 (1.9)	
Vaccinated two doses	14231 (33.4)	30 (34.5)		8124 (26.8)	15 (29.4)	
Vaccinated three doses	18788 (44.1)	11 (12.6)		13172 (43.4)	5 (9.8)	
Vaccinated four doses	4440 (10.4)	4 (4.6)		4062 (13.4)	0 (0)	
Vaccinated five doses	110 (0.3)	0 (0)		284 (0.9)	0 (0)	
Type of primary vaccine series, n (%)	**n = 14231**	**n = 30**		**n = 8124**	**n = 15**	
Sinovac/Sinopharm-ChAdOx1 nCoV-19	4780 (33.6)	7 (23.3)	*0.460*	2690 (33.1)	7 (46.7)	*0.070*
Sinovac–Sinovac or Sinopharm–Sinopharm	1808 (12.7)	4 (13.3)		1201 (14.8)	2 (13.3)	
ChAdOx1 nCoV-19-ChAdOx1 nCoV-19	451 (3.2)	0 (0)		305 (3.8)	1 (6.7)	
Pfizer-BioNTech-Pfizer-BioNTech	1954 (13.7)	6 (20.0)		1292 (15.9)	0 (0)	
ChAdOx1 nCoV-19-Pfizer-BioNTech/Moderna	4319 (30.4)	9 (30.0)		2093 (25.7)	3 (20.0)	
Sinovac/Sinopharm-Pfizer-BioNTech/Moderna	74 (0.5)	0 (0)		55 (0.7)	1 (6.7)	
Moderna–Moderna	845 (5.9)	4 (13.3)		488 (6.0)	1 (6.7)	
Type of third vaccine dose, n (%)	**n = 18788**	**n = 11**		**n = 13172**	**n = 5**	
Pfizer-BioNTech	9958 (53.0)	7 (63.6)	*0.750*	6930 (52.6)	2 (40.0)	*0.780*
ChAdOx1 nCoV-19	4519 (24.1)	3 (27.3)		2790 (21.2)	2 (40.0)	
Moderna	4298 (22.9)	1 (9.1)		3440 (26.1)	1 (20.0)	
Other	13 (0.1)	0 (0)		12 (0.1)	0 (0)	
Type of fourth vaccine dose[a], n (%)	**n = 4439***	**n = 4**		**n = 4062**	**n = 0**	
Pfizer-BioNTech	1950 (43.9)	3 (75.0)	*0.660*	1609 (39.6)	0 (0)	-
ChAdOx1 nCoV-19	163 (3.7)	0 (0)		129 (3.2)	0 (0)	
Moderna	2325 (52.4)	1 (25.0)		2322 (57.2)	0 (0)	
Other	1 (0.02)	0 (0)		2 (0.1)	0 (0)	
Type of fifth vaccine dose, n (%)	**n = 110**	**n = 0**		**n = 284**	**n = 0**	
Pfizer-BioNTech	14 (12.7)	0 (0)	-	238 (83.8)	0 (0)	-
Moderna	96 (87.3)	0 (0)		46 (16.2)	0 (0)	
Median (IQR) time since last vaccination, days	138 (101–176)	137 (118–183)	*0.690*	180 (128–217)	237 (183–261)	*<0.01*

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Table 2 (*continued*)

Variable	BA.2 predominance (N = 42,689)			BA.4/BA.5 predominance (N = 30,371)		
	Without severe COVID-19 outcome	With severe COVID-19 outcome	*p-value*	Without severe COVID-19 outcome	With severe COVID-19 outcome	*p-value*
Time since last vaccination, n (%)						
≤14days	695 (1.9)	1 (2.2)	*0.940*	462 (1.9)	0 (0)	*0.140*
>14—90 days	6918 (19.1)	8 (17.8)		3218 (12.9)	1 (5.0)	
>90—180 days	20342 (56.0)	24 (53.3)		8940 (35.8)	4 (20.0)	
>180 days	8340 (23.0)	12 (26.7)		12327 (49.4)	15 (75.0)	

[a] Vaccine type missing in 1 subject.
IMV = Invasive Mechanical Ventilation, IQR = Interquartile range.

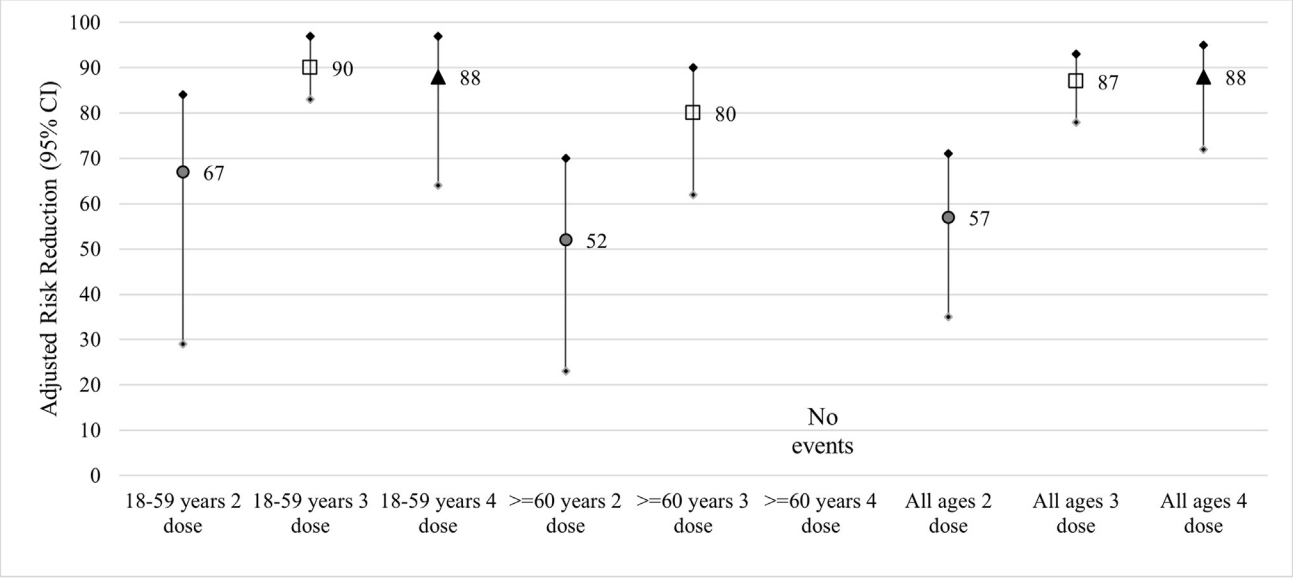

Figure 2. Risk reduction of severe COVID-19 among adults during BA.2 and BA.4/BA.5 omicron predominance, by vaccination regimens stratified by age group.

those who received the third dose 14—90 days had the highest risk reduction (89%, 95% CI 68 to 96%) followed by > 90—180 days (87%, 95% CI 71 to 95%) and >180 days (79%, 95% CI 35 to 71%). Similarly, those who received the primary series 14—90 days prior to the date of positive SARS-CoV-2 test had the highest risk reduction (66%, 95% CI 24 to 91%) and waning was observed from >90 days (47%, 95% CI 13 to 90%) with no protection >180 days. The number of events observed with fourth dose was not sufficient to sub-group by time since last dose to allow meaningful comparisons (Supplementary Table 2, Supplementary Fig. 1).

All three vaccine types used for boosting, Pfizer-BioNTech, ChAdOx1 nCoV-19 and Moderna, offered similar protection against severe COVID-19 with BA.2 and BA.4/BA.5 omicron sub lineages (Supplementary Table 2, Supplementary Fig. 2). Very small proportions of the population in Thailand received three or four dose homologous schedules so to avoid spurious comparisons we have not stratified analyses to evaluate potential differences between heterologous and homologous schedules.

Discussion

While the number of COVID-19 cases and deaths globally remain high, the impact of vaccinations is undisputable, when they have been implemented appropriately. As vaccination schedules have rapidly evolved to third, fourth and even fifth doses to manage newer 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 fifth dose schedules incorporating inactivated vaccines into the primary series.

We found that BA.4/BA.5 omicron sub-lineage was not associated with more severe COVID-19 outcomes or deaths as compared to BA.2. We are aware of only one other publication[14] reporting on clinical severity of BA.4/BA.5, which also showed that BA.4/BA.5 had similar clinical severity to earlier omicron sub-lineages. Sustained protection against newer omicron variants is likely due to high

population immunity due to vaccination and/or previous infection.[23] Good T-cell response underpins this high level of protection against severe infection and death, irrespective of the variants of concern.[24]

Our study found that risk of severe outcomes and deaths against newer omicron sub-lineages were significantly reduced with third (87% (95% CI 78 to 93%) and 95% (95% CI 84 to 98%), respectively) and fourth (88% (95% CI 72 to 95%) and 95% (95% CI 76 to 99%), respectively) dose vaccination, respectively. The level of protection with boosters observed in our study is comparable to observations from Norway, UK and Denmark.[10,25,26] One key finding from our study is that the booster doses continue to offer protection against newer omicron sub-lineages including BA.4/BA.5, and the level of protection was comparable to that offered against severe outcomes in the early omicron period.[21]

We observed some waning of the protective effect of booster doses against severe COVID-19 outcomes, with optimal protection observed with vaccines received 14—90 days prior to the positive SARS-CoV-2 test. Among three-dose recipients, the risk reduction dropped by over 10 percentage points for those vaccinated >180 days prior as compared to 14—90 days prior, while a sharper drop was observed among two dose recipients. Our findings are consistent with studies from the US,[27] Sweden[28] and Malaysia[29] where protection against COVID-19—associated hospitalizations and/or severe outcomes waned after 4-months.

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 with newer omicron sub-lineages. A key feature of Thailand's vaccination programme is its highly heterogenous use of multiple vaccines. As the vast majority of COVID-19 vaccine data analysis has been performed on homogenous schedules, we believe the current data adds significantly to the body of evidence. However, it is also this high heterogeneity, with many different combinations of vaccines that makes it extremely difficult to stratify by specific schedules for analysis. For example, the most widely used homologous priming schedule was Pfizer-BioNTech with only 13—15% uptake. As only ~50% of people took Pfizer-BioNTech as a third dose and less than 50% as a fourth dose, the highest possible proportion of subjects with a four dose homologous schedule is around 3—3.5%. Comparable protection from viral vector vaccines and mRNA-based vaccines against infection, hospitalization, ICU admissions and deaths, has been previously reported, negating the need for an analysis based on homologous vs heterologous stratification.[10,15,21,30] Our findings corroborate this evidence and strongly supports the use of Pfizer-BioNTech, Moderna and ChAdOx1 nCoV-19 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 timely booster vaccinations continue to play a key role in protecting populations against severe COVID-19 outcomes and deaths with newer variants of concern. Accelerating the booster vaccinations and increasing coverage by using any vaccines available, particularly among the elderly is an important strategy to optimize protection.

We wish to highlight a few study limitations. In the current study we were unable to examine other important confounders such as chronic comorbidities which are known 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. The sub-lineage data was not available at individual-level and the molecular evidence published by the Ministry of health on a random sample COVID-19 positive cases from Northern Thailand was used as a proxy to define BA.2 and BA.4/5 predominance.

Author contributions

All authors contributed to the conception and design of the study, SC, KC, TW, WK, 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 manuscript and revising it critically. All authors approved the final version of the manuscript submitted.

Data availability statement

All relevant data is available in the paper. A de-identified dataset and related codes for analysis will be made available to researchers on request. Requests for data should be addressed to the corresponding author (suwat.c@cmu.ac.th).

Declaration of competing interest

SC reports consulting fees from AstraZeneca. All other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.10.001.