

ประสิทธิผลของวัคซีนป้องกันโควิด-19 ในช่วงการระบาดของเดลต้าและโอไมครอนในประเทศไทย: การวิเคราะห์ด้วย Test-negative design แบบถ่วงน้ำหนักคะแนนแนวโน้ม (propensity-score weighting)

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บทคัดย่อ

ความสำคัญ: ถึงแม้จะมีหลักฐานว่าวัคซีนป้องกันโควิด-19 มีความปลอดภัยและมีประสิทธิภาพ แต่การศึกษาประสิทธิผลของวัคซีนในประชากรที่เฉพาะกลุ่มและในช่วงเวลาที่เป็นปัจจุบันมีความจำเป็น

วิธีการศึกษา: เป็นการวิเคราะห์ประสิทธิผลของวัคซีนจากเวชระเบียนจากผู้ป่วยผู้ใหญ่ที่มีอาการจำนวน 90,436 รายที่มารับการรักษาในโรงพยาบาลรัฐฯ สี่แห่งในประเทศไทย ใช้การวิเคราะห์ด้วย Test-negative design แบบถ่วงน้ำหนักคะแนนแนวโน้ม (propensity-score weighting) เพื่อเปรียบเทียบโอกาสของการทดสอบพบเชื้อ SARS-CoV-2 ในผู้ที่ได้รับการฉีดวัคซีนกับผู้ที่ไม่ได้รับการฉีดวัคซีน การประมาณประสิทธิผลของวัคซีน (Vaccine effectiveness: VE) ในการป้องกันโรคในผู้ป่วยที่มีอาการแสดงแยกตามได้รับวัคซีนครบสองเข็ม เข็มกระตุ้นหนึ่งเข็ม สองเข็ม ประเภทของวัคซีนที่ได้รับ เวลาตั้งแต่การฉีดวัคซีนจนพบเชื้อและจำแนกตามในช่วงการระบาดของเดลต้าและโอไมครอน

ผลการศึกษา: ในช่วงการระบาดของเดลต้าประสิทธิผลของวัคซีนในผู้ป่วยที่ได้รับวัคซีนครบสองเข็มเท่ากับ 37% (ช่วงความเชื่อมั่น 95% (CI): 28-44%) และสูงสุดในผู้ที่ได้รับเมื่อได้รับเข็มกระตุ้นสุดท้ายภายใน 90-179 วันก่อนเริ่มมีอาการ ส่วนในช่วงการระบาดของ Omicron ประสิทธิภาพของวัคซีนในผู้ที่ได้รับวัคซีนเข็มกระตุ้นสองครั้ง 24% (95% CI: 15-32%) และสูงสุดเมื่อได้รับวัคซีนกระตุ้นครั้งที่สองในช่วง 14-89 วันก่อนเริ่มมีอาการ 39% (95% CI: 30-47%) พบประสิทธิผลของวัคซีนสูงในผู้ที่ได้รับวัคซีนชนิด mRNA ทั้งช่วงการระบาดทั้ง Delta (90%, 95% CI: 64-97%) และ Omicron (11%, 95% CI: 0-21%)

สรุป: โดยรวมแล้ว พบว่าประสิทธิผลของวัคซีนลดลงจากช่วงการระบาดของเดลต้าถึงโอไมครอน ประสิทธิภาพที่ดีที่สุดพบในช่วงการระบาดของโอไมครอนในผู้ที่ได้รับวัคซีนกระตุ้นครั้งที่สองในระยะ 14-89 วันก่อนเริ่มมีอาการ การค้นพบนี้สนับสนุนการฉีดวัคซีนกระตุ้นเข็มที่ 2 อย่างต่อเนื่องทั่วประเทศไทย และอาจเป็นข้อมูลพื้นฐานสำหรับการออกแบบการฉีดวัคซีนป้องกันโควิด-19 ในระหว่างการติดเชื้อระลอกใหม่ในอนาคต

คำสำคัญ: ประสิทธิผลของวัคซีนป้องกันโควิด-19, case control, แบบถ่วงน้ำหนักคะแนนแนวโน้ม

Effectiveness of COVID-19 vaccines during Delta and Omicron periods in Thailand: A test-negative, propensity score-weighted analysis

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Abstract

Background: Although COVID-19 vaccines have shown to be safe and efficacious, vaccine effectiveness studies are necessary to understand the real-world effectiveness in specific populations and time periods.

Method: We conducted a vaccine effectiveness analysis on medical records from 90,436 symptomatic adults in four public hospitals in Thailand. We used a test-negative design with propensity-score weighting to compare the odds of positive SARS-CoV-2 test among vaccinated individuals to unvaccinated individuals. Vaccine effectiveness (VE) against symptomatic disease was estimated for receipt of primary series, one booster dose, and two booster doses, as well as the type of vaccines received and time since vaccination, during Delta- and Omicron-predominant periods.

Result: During Delta circulation, vaccine effectiveness was 37% (95% confidence interval [CI]: 28-44%) for individuals who had completed a primary series and was highest when the last dose was received 90-179 days before symptom onset. During Omicron, vaccine effectiveness was observed for those who had received two booster doses (24%, 95% CI: 15-32%), and was highest when the second booster dose was received 14-89 days prior to symptom onset (39%, 95% CI: 30-47%). Vaccine effectiveness was highest for completion of an mRNA primary series during both Delta (90%, 95% CI: 64-97%) and Omicron (11%, 95% CI: 0-21%) time periods.

Conclusion: Overall, we observed a decline in vaccine effectiveness from Delta to Omicron time periods; greatest protection during Omicron was seen with the completion of a second booster dose 14-89 days before symptom onset. These findings support continued outreach for

second booster doses throughout Thailand and may inform COVID-19 vaccination schedules during future waves of infection.

Key words: Effectiveness of COVID-19 vaccines, case control study, propensity score-weighted analysis

Introduction

Thailand was the first country to detect SARS-CoV-2 outside of China in January 2021.¹ As of 28 February 2023, there have been 4,728,035 laboratory-confirmed SARS-CoV-2 cases and 33,911 deaths in Thailand.² While vaccination programs have been implemented to contribute to the control of COVID-19, the real-world effectiveness of COVID-19 vaccines against symptomatic disease has varied by variant-predominant period, vaccine products, and the amount of time since vaccination.^{3,4} In February 2021, Thailand began its rollout of COVID-19 vaccines, initially targeting priority populations of healthcare providers, elderly individuals (over 60 years), people in areas with high COVID-19 incidence, pregnant women, and people with comorbidities. Children aged 12-18 were added to the vaccination schedule in August 2021 and were included in the priority populations for vaccination.⁵ By March 2022, an estimated 72% of the population had received at least 2 COVID-19 vaccine doses.⁶ By the end of 2021, Thailand had authorized six COVID-19 vaccines for use. The first authorized vaccine was CoronaVac (Sinovac) in February 2021, followed by ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and mRNA-1273 (Moderna) in May 2021, BNT162b2 (Pfizer/BioNTech) and BBIBP-CorV (Sinopharm) in June 2021, and Ad26.COV2.S (Janssen) in October 2021.⁷ The most commonly administered vaccines for a primary series in Thailand have been CoronaVac and ChAdOx1 nCoV-19, and “mix-and-match” regimens for both primary series and booster doses have been approved since July 2021.⁴ While approved vaccines have shown to be efficacious in clinical trials.⁸, there has been limited global research on the use of heterologous COVID-19 vaccine regimens, as is common in Thailand.

Since the rollout of COVID-19 vaccines, the test-negative design has become a common method to estimate the real-world vaccine effectiveness (VE) of COVID-19 vaccines.⁹ The test-negative design has traditionally been used as a form of case-control study to assess the effectiveness of influenza vaccines, often through existing surveillance systems.^{10,11} Benefits of the test-negative design include the reduction of bias due to differences in healthcare-seeking

behavior between vaccinated and unvaccinated individuals, and its adaptability of use to apply to different pathogens or populations.¹² During the COVID-19 pandemic, the test-negative design has been used to generate quick estimates of vaccine effectiveness in specific geographic and social settings. However, several challenges have been noted on the application of the test-negative design to the COVID-19 vaccines, including variations in the likelihood to seek testing for COVID-19, misclassification of cases and controls due to asymptomatic infection or prolonged RNA shedding, and differences in adherence to nonpharmaceutical interventions between vaccinated and unvaccinated individuals.¹³ Strict inclusion criteria, along with adjustment of potential confounders through methods such as propensity score weighting, can reduce the effects of bias on COVID-19 VE estimates.^{14,15}

As SARS-CoV-2 continues to evolve, it will be prudent to continue monitoring the real-world effectiveness of varying doses and types of COVID-19 vaccines. Although other test-negative studies have been conducted in Thailand¹⁶⁻¹⁷, we aim to provide additional data using a propensity-score weighted analysis. To our knowledge, our analysis is the first in Thailand to use propensity-score weighting; we adjust for a wider range of covariates to counteract known limitations of test-negative studies.¹⁸ We describe VE of symptomatic COVID-19 infection in Thailand according to the number of vaccine doses and the type of vaccine product(s) received during Delta- and Omicron-predominant periods.

Methods

Study design and inclusion

We used a test-negative design to assess the effectiveness COVID-19 vaccines against symptomatic illness among individuals of Thai nationality and ≥ 18 years of age presenting to four hospitals in Thailand including Maechan hospital, Nakhon Phanom hospital, Prapokklao hospital, and Samui hospital.

Data sources

This study used routinely collected data from a hospital registries database for individuals seeking care in public hospitals in Thailand. Datasets containing demographic and clinical information on individuals who were tested for SARS-CoV-2 between July 2021-October 2022 were obtained from each of the four hospitals. Individual-level data were extracted from

datasets, including age, sex, comorbidities, COVID-19 vaccination status, and the frequency of hospital visits. The datasets were linked with the national vaccination database and laboratory test results using unique patient identifiers. For analysis, vaccination status was categorized as unvaccinated, completed primary series, received 1 booster dose, or received 2 booster doses. Vaccine types were described as inactivated (Sinovac, Sinopharm), viral vector (Oxford/AstraZeneca), or mRNA (Pfizer/BioNTech, Moderna). Patients were excluded from the analysis if they had only partially completed a primary series, had received the most recent vaccination dose <14 days prior to hospital presentation or symptom onset, or if symptom onset was >10 days prior to hospital presentation.

In Thailand, clinical guidelines for SARS-CoV-2 testing and treatment were uniform throughout the country but changed over time. In each of the four hospitals included in this analysis, patients were tested for SARS-CoV-2 via RT-PCR and/or antigen test if they presented with any of the known symptoms of COVID-19 or were close contacts of SARS-CoV-2 positive individuals, according to the case definitions and clinical guidelines issued by the Ministry of Public Health.^{19,20} For this analysis, we used data on symptomatic patients only; criteria for eligible symptoms for testing were subject to national guidelines and hospital standards.

Statistical analysis

The test-negative design was used to compare the odds of positive SARS-CoV-2 RT-PCR test among vaccinated individuals with the odds among unvaccinated individuals. Vaccine effectiveness (VE) was calculated as: $VE = (1 - \text{adjusted odds ratio}) * 100\%$. For the primary analysis on VE against symptomatic illness, cases were defined as symptomatic individuals who tested positive for SARS-CoV-2 via RT-PCR; controls were defined as symptomatic individuals who tested negative for SARS-CoV-2 via RT-PCR. Descriptive analyses were conducted comparing baseline characteristics between cases and controls, and the number of COVID-19 vaccine doses received. Standardized mean differences were reported. We stratified vaccine effectiveness estimates by variant-predominant period: Delta period was defined as hospital presentation between July 2021–December 2021, and Omicron period was defined as hospital presentation between January 2022–October 2022. We created propensity-for-vaccination scores for each of the variant-predominant periods considering the following variables: sex, age (18–59 and ≥ 60), presence of comorbidities, frequency of hospital visits (categorized into quintiles based on medical records), hospital location, and calendar time (defined as weeks since July 1, 2021).

Propensity score weights were calculated using the inverse of the probability to receive vaccine doses when compared to unvaccinated individuals. Separate propensity scores were created for each tier of vaccination status: completion of primary series, 1 booster dose, and 2 booster doses. Variables with an unweighted standardized mean difference (SMD) >0.1 or <-0.1 were considered for inclusion into propensity score models; balance of covariates was achieved with a weighted SMD <0.1 or >-0.1 . Unbalanced covariates with a weighted SMD >0.2 or <-0.2 were removed from the propensity score model and instead included as covariates in multivariable logistic regressions, a method that has been employed in other test-negative studies.^{14,21} Calendar time was included as an a priori variable in all propensity score weights and included as a covariate in logistic regressions if the weighted SMD was >0.2 or <-0.2 . For our primary analysis, we estimated VE according to the number of doses received (primary series only, primary series + one booster, and primary series + two boosters) during Delta- and Omicron-predominant periods. For each variant-predominant period, we stratified VE by the amount of time from the most recent dose to symptom onset (14-89 days, 90-179 days, and 180+ days). Three-month intervals were defined based on commonly used cutoffs in other COVID-19 vaccine effectiveness studies.¹⁶

In our secondary analysis, we estimated VE according to the type of vaccine received during each variant-predominant period. We estimated VE for homologous primary series of inactivated, viral vector, and mRNA vaccine products, as well as heterologous primary series. We also estimated VE for individuals who had received one or two booster doses based on the type of vaccine received for the most recent booster dose: inactivated, viral vector, or mRNA vaccine. All adjusted odds ratios were calculated through multivariable logistic regression including propensity-for-vaccination weights and/or adjustment for covariates as described above.

All analyses were conducted using Stata version 17 (StataCorp LLC). This study was a program evaluation of the COVID-19 pandemic using an administrative database from the Division of Epidemiology, Department of Disease Control, Ministry of Public Health.

Results

From July 2021 – October 2022, 90,436 patients meeting the inclusion criteria were tested for COVID-19. During the Delta-predominant period, 3,325 cases were identified (9% positivity); during the Omicron-predominant period, 19,164 cases were identified (35% positivity). Unvaccinated individuals accounted for 72% and 30% of patients during Delta and Omicron, respectively. Additional baseline characteristics of patients are reported in Table 1.

Table 1 Baseline characteristics by laboratory confirmed (RT-PCR) SARS-CoV-2 infection status and Covid-19 vaccination status from July 2021 – October 2022 from four hospitals, Thailand.

	Total	Covid-19 status		SMD ^a	Covid-19 vaccine status				SMD ^a
		Cases*	Controls		Unvaccinated	Completed primary series (A)	(A) + one booster dose	(A)+two booster doses	
	n = 90,436	n = 22,489 (%) ^b	n = 67,947 (%) ^b						
Sex									
Male	41,556	8,440 (20)	33,116 (80)	0.228	21,387 (52)	12,272 (30)	4,540 (11)	1,017 (3)	0.195
Female	48,880	14,049 (29)	34,831 (71)		20,420 (42)	16,539 (34)	6,761 (14)	2,813 (6)	
Age (years)									
Mean (SD)	43 (17)	44 (17)	43 (17)	-0.113	44 (18)	43 (17)	42 (15)	38 (11)	0.074
Median (IQR)	41 (29-55)	42 (30-57)	40 (28 -54)		41 (29-55)	41 (28-55)	40 (29-53)	37 (29-45)	

Age group									
18 – 59 years	74,126	17,850 (24)	56,276 (76)	-0.088	33,753 (46)	23,244 (31)	9,596 (13)	3,765 (5)	0.103
60 years and older	16,310	4,639 (28)	11,671 (72)		8,054 (49)	5,567 (34)	1,705 (10)	65 (0.4)	
Comorbidity ^c									
Yes	14,829	3,666 (25)	11,163 (75)	0.004	8,021 (54)	4,474 (30)	1,422 (10)	323 (2)	0.123
No	75,607	18,823 (25)	56,784 (75)		33,786 (45)	24,337 (32)	9,879 (13)	3,507 (5)	
Frequent of hospital visit									
Quintile 1 (Not Often)	41,381	11,622 (28)	29,759 (72)	0.133	24,232 (59)	10,918 (27)	3,331 (8)	807 (2)	- 0.520
Quintile 2	14,920	3,181 (21)	11,739 (79)		6,159 (41)	5,493 (37)	1,850 (12)	243 (2)	
Quintile 3	12,912	2,968 (23)	9,944 (77)		4,186 (32)	5,481 (43)	2,414 (19)	251 (2)	
Quintile 4	11,366	2,723 (24)	8,643 (76)		3,809 (34)	4,121 (36)	2,163 (19)	844 (7)	
Quintile 5 (Most often)	9,857	1,995 (20)	7,862 (80)		3,421 (35)	2,798 (28)	1,543 (16)	1,685 (17)	
Hospitals									
Nakhon Phanom hospital	47,250	10,107 (21)	37,143 (79)	-0.447	12,174 (26)	19,677 (42)	9,045 (19)	2,747 (6)	0.456
Prapokklao hospital	20,140	3,252 (16)	16,888 (84)		17,603 (87)	1,920 (10)	237 (1)	160 (0.8)	
Maechan hospital	17,366	5,013 (29)	12,353 (71)		9,643 (56)	4,978 (29)	1,339 (8)	681 (4)	
Samui hospital	5,680	4,117 (73)	1,563 (28)		2,387 (42)	2,236 (39)	680 (12)	242 (4)	

Vaccine product received for primary series									
Homologous	11,442	3,492 (31)	7,950 (69)	-0.180	-	11,442 (100)	-	-	-
Inactivated	6,955	2,463 (35)	4,492 (65)	-0.237	-	6,955 (100)	-	-	-
Viral Vector	2,590	546 (21)	2,044 (79)	0.017	-	2,590 (100)	-	-	-
mRNA	1,897	483 (25)	1,414 (75)	-0.036	-	1,897 (100)	-	-	-
Heterologous	17,369	4,621 (27)	12,748 (73)	-0.107	-	17,369 (100)	-	-	-
Vaccine product received for last booster dose									
Inactivated	766	570 (74)	196 (26)	-0.297	-	-	729 (95)	37 (5)	-
Viral Vector	3,549	798 (22)	2,751 (78)	-0.003	-	-	3,468 (98)	81 (2)	-
mRNA	9,590	2,570 (27)	7,020 (73)	-0.096	-	-	6,429 (67)	3,161 (33)	-
Stratified by Variant predominant period									
-B.1.617.2 (Delta)	34,988	3,325 (9)	31,663 (91)	-	25,204 (72)	7,421 (21)	834 (2)	3 (0.01)	-
-B.1.1529 (Omicron)	55,448	19,164 (35)	36,284 (65)	-	16,603 (30)	21,390 (39)	10,467 (19)	3,828 (7)	-

^aSMD = standardized mean difference, ^bRow percent, ^cAny of the following comorbidities: diabetes mellitus, hypertension, heart diseases, asthma, COPD, cerebrovascular diseases, chronic kidney diseases, hematologic disorders, neuromuscular disorders, cancer, *positive for RT-PCR confirmed SARS-CoV-2 infection.

In each of the VE models, frequency of hospital visits, hospital location, and calendar time were included either in propensity score weights or as covariates in multivariable models. The inclusion of sex, age, and comorbidities into models was dependent on differences between vaccinated and unvaccinated persons and varied between models. The estimated VE against symptomatic disease in persons who received a primary series, one booster, and two booster doses of any vaccine type are shown in Table 2. During the Delta-predominant period, VE was 37% (95% CI: 28-44%) among individuals who had completed a primary series of any vaccine type and was not significant among individuals who had received one booster dose. Only three individuals in the analysis group had received two booster doses during the Delta period, so effectiveness was not able to be calculated. Among individuals who had received a primary series, effectiveness was highest with 90-179 days between the last dose and symptom onset (61%, 95% CI: 47-71%). During the Omicron-predominant period, VE was observed among individuals who had received 2 booster doses (24%, 95% CI: 15-32%). VE was estimated to be ineffective among those who had received a primary series only or one booster dose. In patients who had received a primary series only, VE was 13% (95% CI: 6-19%) when the last dose was received 14-89 days before hospital presentation. VE was also observed in patients who had received two booster doses, with the last dose occurring 14-89 days before hospital presentation (39%, 95% CI: 30-47%).

Table 2: Estimated vaccine effectiveness against laboratory-confirmed SARS-CoV-2 infection from July 2021– October 2022, stratified by variant-predominant period, according to vaccination status.

	No. of patients	Positive for SARS-CoV-2 no. (%)	Adjusted odds ratio (95%CI) ^a	VE (95%CI)	p-value
Variant predominant period					
<i>B.1.617.2 (Delta)</i>					
-Unvaccinated	25,204	2,614 (10.4)	Ref.	-	-
-Primary series	7,421	491 (6.6)	0.63 (0.56, 0.72)	37 (28, 44)	< 0.001

-Primary series + one booster	834	108 (13.0)	1.38 (0.85, 2.24)	-38 (-124, 15)	0.196
-Primary series + two boosters	3	0 (0.0)	-	-	-
<i>Time from last dose to symptom onset (days)</i>					
-Unvaccinated	25,204	2,614 (10.4)	Ref.	-	-
<i>Primary series</i>					
-14 – 89	5,613	393 (7.0)	0.69 (0.61, 0.79)	31 (21, 39)	< 0.001
-90 - 179	1,665	70 (4.2)	0.39 (0.29, 0.53)	61 (47, 71)	< 0.001
-≥ 180	143	28 (19.6)	1.62 (1.04, 2.52)	-62 (-152, -4)	0.032
<i>Primary series with one booster</i>					
-14 – 89	682	107 (15.7)	1.48 (0.92, 2.37)	-48 (-137, 8)	0.105
-90 - 179	152	1 (0.7)	0.24 (0.03, 1.67)	76 (-67, 97)	0.149
-≥ 180	0	0	-	-	-
<i>-Primary series + two boosters</i>					
-14 – 89	3	0 (0.0)			
-90 - 179	-	-	-	-	-
-≥ 180	-	-	-	-	-
<i>Variant predominant period</i>					
<i>Omicron</i>					
-Unvaccinated	16,603	6,713 (40.4)	Ref.	-	-
-Primary series	21,390	7,622 (35.6)	1.38 (1.31, 1.46)	-38 (-46, -31)	< 0.001
-Primary series + one booster	10,467	3,224 (30.8)	1.85 (1.72, 1.99)	-85 (-99, -72)	< 0.001

-Primary series + two boosters	3,827	863 (22.6)	0.76 (0.68, 0.85)	24 (15, 32)	< 0.001
<i>Time from last dose to symptom onset (days)</i>					
Unvaccinated	16,603	6,713 (40.4)	Ref.	-	-
<i>Primary series</i>					
-14 – 89	5,103	1,394 (27.3)	0.87 (0.81, 0.94)	13 (6, 19)	< 0.001
-90 - 179	9,774	3,325 (34.0)	1.19 (1.12, 1.27)	-19 (-27, -12)	< 0.001
≥ 180	6,511	2,903 (44.6)	2.16 (2.01, 2.31)	-116 (-131, -101)	< 0.001
<i>Primary series with one booster</i>					
-14 – 89	6,406	1,692 (26.4)	1.19 (1.10, 1.29)	-19 (-28, -10)	< 0.001
-90 - 179	3,206	1,231 (38.4)	2.90 (2.61, 3.21)	-190 (-221, -161)	< 0.001
≥ 180	855	301 (35.2)	2.82 (2.02, 3.93)	-182 (-293, -102)	< 0.001
<i>-Primary series + two boosters</i>					
-14 – 89	2,596	500 (19.0)	0.61 (0.53, 0.70)	39 (30, 47)	< 0.001
-90 - 179	1,166	305 (26.1)	1.05 (0.86, 1.29)	-5 (-29, 14)	0.612
≥ 180	61	57 (93.4)	1.29 (0.39, 4.30)	-29 (-303, 61)	0.674

During the Omicron-predominant period, VE against symptomatic illness was 11% (95% CI: 0–21%) for homologous mRNA primary series. Inactivated vaccines were shown to be ineffective at preventing symptomatic illness, and VE for viral vector vaccines was not significant. Additionally, effectiveness was not observed when analyzing which vaccine product was received for the last booster dose.

Table 3: Estimated vaccine effectiveness against laboratory-confirmed SARS-CoV-2 infection from July 2021–October 2022, stratified by variant-predominant period, according to vaccination products.

	No. of patients	Positive for SARS-CoV-2 no. (%)	Adjusted odds ratio (95%CI) ^a	VE (95%CI)	P-value
Variant predominant period					
<i>B.1.617.2 (Delta)</i>					
<i>Unvaccinated</i>	25,204	2,614 (10.4)	Ref.	-	-
<i>Vaccine product received for primary series</i>					
Homologous	3,995	296 (7.4)	0.67 (0.58, 0.79)	33 (21, 42)	< 0.001
Inactivated	2,920	255 (8.7)	0.75 (0.63, 0.89)	25 (11, 37)	0.001
Viral Vector	889	38 (4.3)	0.67 (0.45, 0.99)	33 (1, 55)	0.050
mRNA	185	3 (1.6)	0.10 (0.03, 0.36)	90 (64, 97)	< 0.001
Heterologous	3,426	195 (5.7)	0.66 (0.56, 0.78)	34 (22, 44)	< 0.001
<i>Vaccine product received for last booster dose</i>					
Inactivated	141	21 (14.9)	1.42 (0.80, 2.51)	-42 (-151, 20)	0.230
Viral Vector	389	30 (7.7)	0.88 (0.51, 1.52)	12 (-52, 49)	0.638
mRNA	307	57 (18.6)	2.00 (1.45, 2.75)	-100 (-175, -45)	< 0.001
Variant predominant period					
<i>Omicron</i>					
<i>Unvaccinated</i>	16,603	6,713 (40.4)	Ref.	-	-
<i>Vaccine product received for primary series</i>					

	No. of patients	Positive for SARS-CoV-2 no. (%)	Adjusted odds ratio (95%CI) ^a	VE (95%CI)	P-value
Homologous	7,447	3,196 (42.9)	2.05 (1.92, 2.19)	-1.05 (-119, -92)	< 0.001
Inactivated	4,035	2,208 (54.7)	3.39 (3.12, 3.68)	-239 (-268, -212)	<0.001
Viral Vector	1,701	508 (30.0)	0.99 (0.88, 1.11)	1 (-11, 12)	0.865
mRNA	1,712	480 (28.0)	0.89 (0.79, 1.00)	11 (0, 21)	0.052
Heterologous	13,943	4,426 (31.7)	1.08 (1.02, 1.15)	-8 (-15, -2)	0.005
<i>Vaccine product received for last booster dose</i>					
Inactivated	625	549 (87.8)	17.06 (11.46, 25.39)	-1,606 (-2,536, -1,046)	< 0.001
Viral Vector	3,160	768 (24.3)	1.10 (0.98, 1.23)	-10 (-23, 2)	0.102
mRNA	9,291	2,513 (27.1)	1.29 (1.19, 1.39)	-29 (-39, -19)	<0.001

Discussion

In this analysis of COVID-19 vaccine effectiveness in four public hospitals in Thailand, we found declining effectiveness against symptomatic disease from Delta- to Omicron-predominant periods, after adjusting for propensity to be vaccinated during each time period. Our analysis showed higher VE among those who had received a homologous mRNA primary series compared to inactivated, viral vector, or heterologous primary series regimens. These findings are consistent with current knowledge on decreased vaccine effectiveness against the B.1.1529 (Omicron) strain³, and varying effectiveness based on demographic characteristics and types of vaccine product received.²²

During the Delta-predominant period, VE was observed among individuals who had received a primary series, but not among those who had received a booster dose. This is likely due to the

fact that the proportion of individuals who had received a booster dose during Delta was low (834 patients) compared to those who had only received a primary series (7,421 patients). These observations are consistent with the timing of vaccine rollout in Thailand; in general, the number of third (booster) doses administered did not increase significantly until 2022.²³ The lower sample size of boosted individuals during Delta may have impacted the power to detect effectiveness against symptomatic disease.

Several VE estimates during the Delta-predominant period were statistically significant, but showed ineffectiveness at preventing symptomatic disease. There may be several reasons VE was estimated to be ineffective. While this analysis used propensity score weighting to adjust for covariates that influence vaccination, there may have been unmeasured characteristics and behaviors that influenced the propensity to receive COVID-19 vaccines, and thus could impact VE estimates. This analysis showed that receipt of a primary vaccine series was ineffective at preventing symptomatic illness when the last dose was received ≥ 180 days prior to the hospital visit. It is common to observe waning VE several months after vaccination; several studies during the Delta period have also documented reduced VE over time.⁴ Our estimates may have also been impacted by the small sample size of individuals who received the last dose of their primary series ≥ 180 days prior to the hospital visit ($n=143$ patients, compared to 25,204 unvaccinated individuals). Receipt of mRNA vaccines as the last booster dose also showed to be ineffective at preventing symptomatic illness; this finding should be interpreted with caution, as this estimate did not consider the types of vaccines received for the first two doses. Effectiveness of booster doses may vary based on the vaccines received for a primary series²⁴; future studies may provide further insights by considering the total combinations of vaccine types received.

We found low effectiveness of COVID-19 vaccines against symptomatic illness during the Omicron-predominant period, which reflects the findings of another test-negative analysis conducted in Thailand during Omicron.¹⁶ Multiple studies have identified decreased severity of the Omicron lineage compared to Delta, as well as an increased ability to evade immune protection^{25,26}, which has led to more vaccinated individuals infected with mild illness. While COVID-19 vaccines have shown to be effective at preventing severe illness and death during

Omicron, there has been a decreased ability of vaccines to prevent symptomatic illness^{3,16} Since the clinical criteria for suspected cases in Thailand included additional symptoms during Omicron compared to Delta^{19,20}, a greater proportion of mildly symptomatic individuals were likely tested during the Omicron period. Data used in our analysis, then, may have represented milder cases during Omicron compared to Delta, especially among vaccinated individuals. A greater likelihood of detecting mild cases during Omicron due to epidemiologic factors and clinical criteria could have impacted the reduction of VE estimates during Omicron.

Despite the lower vaccine effectiveness observed during Omicron, individuals with 2 booster doses had some protection against symptomatic disease, especially in the first 90 days following vaccination. These findings support the promotion of 2nd booster doses throughout Thailand, and may inform planning for future vaccine promotion based on expected transmission cycles of SARS-CoV-2 during the endemic stage.

During Omicron, several VE estimates showed COVID-19 vaccines to be ineffective at preventing symptomatic disease. The Omicron period coincided with large-scale reopening of the country and loosening of COVID-19 restrictions in Thailand²⁷, which may have impacted behaviors that increase risk of COVID-19 transmission. Vaccinated individuals may have been more likely to seek testing for mild illness, which could bias VE estimates. Further VE analyses with stricter inclusion criteria may provide more reliable estimates, especially with the circulation of milder variants. As COVID-19 transitions to endemicity, assessing the effectiveness of vaccines against severe outcomes will be more beneficial for policy and public health implications than assessing the effectiveness against symptomatic disease.

In both Delta- and Omicron-predominant periods, mRNA vaccines were found to be the most effective vaccine type received for a primary series, which is consistent with findings of other recent studies.^{3,22} While estimates for the type of vaccine received for the last booster doses were inconclusive, effectiveness may have been impacted by the combinations of vaccine products received, as has been shown in studies investigating the effectiveness of different vaccine combinations in Thailand.²⁸ Future analyses can further investigate effectiveness of different combinations of primary series and booster doses. However, the greater effectiveness

of mRNA vaccines in a homologous primary series may help to inform national recommendations for COVID-19 vaccination moving forward.

Although our study has strengths in the propensity-score weighting approach, there are several limitations to our methodology and findings. First, we did not have the ability to assess specific severity indicators of COVID-19 infection such as mechanical ventilation or death. Our only indicator for severity was hospital admission, which may have been indicative of a variety of illness severities, as hospitalization was recommended for most COVID-19 positive individuals who were at risk for severe disease in Thailand, even when only mild symptoms were reported.^{19,20} Future studies in Thailand should consider additional measures of VE against severe disease and death, to generate a more complete picture of the benefits to COVID-19 vaccination. Second, inclusion into our analysis was based on hospitals' criteria for COVID-19 testing rather than a specific case definition. While all individuals in our sample were symptomatic, testing decisions were ultimately up to the hospitals' discretion, and may not have been consistent throughout time. Although we accounted for differences by adjusting estimates for calendar time and hospital location, unmeasured differences in the decision to test patients may have resulted in selection bias, and vaccine effectiveness estimates should be interpreted with caution. Third, although we used both propensity-score weighting and adjustment of covariates in multivariable models, our estimates may be subject to residual confounding. For instance, we did not consider occupation or educational level in our analysis. Several occupations including healthcare workers may have increased likelihood of exposure to COVID-19 and increased propensity for vaccination, and failure to account for these differences could bias results. Fourth, while the test-negative design can reduce confounding due to healthcare-seeking behavior, there may have been unmeasured differences in the likelihood to seek care for COVID-like illness between vaccinated and unvaccinated individuals. In Thailand, the popularity of at-home testing with antigen test kits may have impacted the likelihood to seek confirmatory testing at hospitals for vaccinated and unvaccinated individuals differently. As other studies have indicated, treatment-seeking bias can be present in test-negative studies if the severity of illness differs between vaccinated and unvaccinated individuals.^{21,22} Even though we considered the frequency of previous hospital visits in our analysis, potential differences in care-seeking specific to COVID-19 could have impacted VE estimates. Finally, the VE estimates

for booster doses by vaccine product should be interpreted with caution. Since we only considered which type of vaccine was received for the most recent booster dose, instead of the total combination of products received, the VE estimates may not be applicable to the entire population who have received booster doses. With many possibilities for vaccine combinations in Thailand, future studies can evaluate differences in VE based on the specific types of doses received.

Conclusion

As the application of the test-negative design relating to COVID-19 vaccine effectiveness is being explored, it is useful to explore different methodologies for calculating real-world vaccine effectiveness while accounting for the limitations of test-negative analyses. Our analysis adds to the existing literature on vaccine effectiveness in Thailand by implementing a propensity-score weighting approach to account for confounding variables during different periods of time. Our findings of waning vaccine effectiveness from Delta to Omicron, as well as the comparative effectiveness of different types of vaccines, may be useful to reference as new vaccine schedules are considered for the endemic stage of COVID-19.

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