Breakthrough infections, hospital admissions, and mortality after major COVID-19 vaccination profiles: a prospective cohort study

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Summary

Background Several COVID-19 vaccination rollout strategies are implemented. Real-world data from the large-scale, government-mandated Central Vaccination Center (CVC), Thailand, could be used for comparing the breakthrough infection, across all available COVID-19 vaccination profiles.

Methods This prospective cohort study combined the vaccine profiles from the CVC registry with three nationally validated outcome datasets to assess the breakthrough COVID-19 infection, hospitalization, and death among Thais individuals who received at least one dose of the COVID-19 vaccine. The outcomes were analyzed by comparing vaccine profiles to investigate the shot effect and homologous effect.

Findings Of 2,407,315 Thais who had at least one dose of COVID-19 vaccine, 63,469 (2.75%) had breakthrough infection, 42,001 (1.79%) had been hospitalized, and 431 (0.02%) died. Per one vaccination shot added, there was an 18% risk reduction of breakthrough infection (adjusted hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.80–0.82), a 25% risk reduction of hospitalization (HR 0.75, 95% CI 0.73–0.76), and a 96% risk reduction of mortality (HR 0.04, 95% CI 0.03–0.06). The heterologous two-shot vaccine profiles had a higher protective effect against infection, hospitalization, and mortality compared to the homologous counterparts.

Interpretation COVID-19 breakthrough infection, hospitalization, and death differ across vaccination profiles that had a different number of shots and types of vaccines.

Funding This study did not involve any funding.

Abbreviations: CVC, central vaccination center; PEC, primary eligibiligy criteria; VV, viral vector vaccine; MR, mRNA vaccine; IN, inactivated vaccine; Co-Lab, Thai COVID-19 infection dataset; CO-Ward, Thai COVID-19 hospitalization dataset; VSDMC, Vaccine Safety and Data Monitoring Committee; PDPA, Personal Data Protection Act; AZ, ChAdOx1 nCoV-19, Vaxzevria, Cambridge, AstraZeneca, UK; PZ, BNT162b2, Comirnaty, BioNTech, Mainz, Germany; SV, CoronaVac, Sinovac Biotech, Beijing, China; MN, mRNA-1273, Moderna, NIAID, USA; RT-PCR, reverse transcription-polymerase chain reaction; IgG, immunoglobulin G; SP, Sinopharm, Beijing Institute of Biological Products, China

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Research in context

Evidence before this study

We searched PubMed and Embase up to June 10, 2021, for relevant peer-reviewed articles on the COVID-19 breakthrough infection, hospitalization, and mortality, using the search terms ("COVID-19" OR "Coronavirus" OR "SARS-CoV-2") AND ("breakthrough infection" OR "hospitalization" OR "death" OR "mortality"). Despite several articles on real-world data for COVID-19 breakthrough infection, none was a large-scale, government-mandated centralized COVID-19 mass vaccination rollout strategy for both service and informatics. Recently, there was a publication from Thailand with a case–control study design. However, there was no prospective cohort study from Thailand.

Added value of this study

Our cohort of government-mandated, large-scale centralized COVID-19 mass vaccination rollout utilized COVID-19 infection, hospitalization, and mortality from centralized informatics from May 24, 2021, to January 31, 2022. The study revealed real-world evidence of COVID-19 breakthrough infection, hospitalization, and mortality in Thailand, an upper-middle income country in Southeast Asia. The potential marginal shot effect and homologous effect were observed for breakthrough infection, hospitalization, and mortality whereas the participants who received more doses of vaccination had lower breakthrough infection rates, hospitalization rates, and mortality rates compared to those with fewer doses of COVID-19 vaccination. The homologous two-shot vaccine profiles had a lower protective effect for breakthrough infection, hospitalization, and mortality compared to the heterologous counterparts.

Implications of all the available evidence

This study provided evidence on the marginal shot effect and homologous effect in a unique real-world setting in an upper-middle income country with a large-scale, government-mandated COVID-19 mass vaccination rollout strategy with a prospective cohort study design. While there were several randomized controlled trials and some real-world data from another setting, this study was complementary to the existing evidence and filled in the gap of knowledge with consistent results. In midst of misinformation and non-generalizability due to different contexts, this evidence would provide both the healthcare professionals and the public in countries with a similar situation with a reliable expectation and plausible explanation for the effectiveness of COVID-19 vaccines on breakthrough infection, hospitalization, and mortality.

Introduction

COVID-19 mass vaccination rollout strategies were different across countries. While most countries have utilized government-mandated large public buildings or areas for mass vaccination, the United States emphasized the strength of a decentralized healthcare system using pharmacies and retail stores as vaccination sites.[1] Canada is one of the countries that have fully decentralized vaccination rollout strategies for both services and informatics,[2] while Chile and Israel have decentralized vaccination services, but keep the databases centrally managed.[3–5] Malta has successfully implemented the COVID-19 mass vaccination with small-scale centralized vaccination services, but the data collection method was not mentioned.[6] To our knowledge, Thailand is the only country that has implemented the large-scale, government-mandated centralized COVID-19 mass vaccination rollout for both service and informatics.

Early studies on COVID-19 vaccines were randomized controlled trials with placebo control, followed by a network meta-analysis to provide evidence comparing vaccine profiles indirectly.[7] There were systematic reviews comparing vaccine effectiveness, but most included studies comparing two vaccines head-to-head.[8,9] Some studies compared more than two vaccine profiles, including one trial in the UK that comparatively investigated efficacies across as many as 7 profiles, but only the safety and immunogenicity were assessed.[10]

Recently, there was increasing heterologous vaccination in several countries due to various reasons—including vaccine shortage and hesitancy—thus emphasizing the need for real-world data.[11] The Central Vaccination Center (CVC) in Thailand is the centralized COVID-19 vaccination center that contained data from a prospective cohort of vaccinated Thais. The CVC registry, combined with the other standardized national infection, hospitalization, and death datasets allows us to comparatively investigate the breakthrough infection across all available COVID-19 vaccination profiles. This study aimed to (1) compare breakthrough infection, hospitalization, and death of individuals who received different major COVID-19 vaccination profiles, (2) investigate the potential marginal benefit of each shot of the COVID-19 vaccine, and the interval effectiveness of major vaccines.

Methods

Study design

This prospective cohort study started on May 24, 2021, which was the launch date of the national COVID-19 centralized vaccination rollout at the CVC in Bangkok,

Thailand. All Thai individuals were entitled to the offered COVID-19 vaccine free of charge if they met the primary eligibility categories (PEC).

Five COVID-19 vaccines were included: ChAdOx1 nCoV-19 (AZ, Vaxzevria, Cambridge, AstraZeneca, UK), mRNA-1273 (MN, Moderna, NIAID, USA), BNT162b2 (PZ, Comirnaty, BioNTech, Mainz, Germany), CoronaVac (SV, Sinovac Biotech, Beijing, China), and BBIBP-CorV (SP, Sinopharm, Beijing Institute of Biological Products, China). COVID-19 vaccines were then categorized based on the type of vaccine; the BBIBP-CorV vaccine was combined with CoronaVac to represent the inactivated COVID-19 vaccines (IN), ChAdOx1 nCoV-19 represented viral vector vaccine (VV), and the mRNA-1273 vaccine was combined with BNT162b2 to represent the mRNA vaccine (MR). All vaccines were administered intramuscularly. The vaccination profiles were categorized into four categories for analysis including (1) First-Shot which was any participant who received only one dose of COVID-19 vaccine at a specific time, (2) Second-Shot Homologous which was any participant who received the same two doses of COVID-19 vaccine at the specific time, (3) Second-Shot heterogenous which was any participant who received different two doses of COVID-19 at the specific time, and (4) Third-Shot which was any participant who received any three doses of COVID-19 at the specific time. Participants with Fourth-Shot, which was any participant who received four doses of any COVID-19 vaccine at a specific time, were limited and the information after receiving Fourth-Shot was excluded from the analysis. Marginal 'shot' effectiveness of major vaccines was defined as the difference in effectiveness per one dose increment regardless of vaccine type.

The CVC has been operated by several institutes under the Department of Medical Services, Ministry of Public Health. The Institute of Dermatology has been responsible for the CVC registry. The vaccine profiles, including the received vaccine, date, and dosage for each dose, as well as individual demographics were retrieved for the analyses. For participants who received any COVID-19 vaccination prior visited the CVC, we also obtained the vaccination records and included them in the analyses.

Study outcomes

The primary outcomes were infection, hospitalization, and death due to COVID-19. The CVC registry was merged with three outcome datasets: (1) COVID-19 Infection (Co-Lab), (2) COVID-19 Hospitalization (CO–Ward), and (3) Death Registry. The breakthrough infection was defined by a positive laboratory test by either real-time reverse transcription-polymerase chain reaction (real-time RT-PCR) or a rapid antigen test (first used in Co-Lab system on August 11, 2021) in patients who received at least one dose of any COVID-19 vaccination. As of January 31, 2022, Co-Lab and CO–Ward contained data on 1,912,786 infections and 1,668,582 admissions, respectively, and were reported by healthcare professionals, and validated and managed by the Ministry of Public Health. The Death Registry was validated with the cause of death from death certification and managed by the Ministry of Interior.

Ethical consideration and personal data protection

The Institutional Review Board, Institute of Dermatology approved the study (IRB No.005/2565). The participants provided written informed consent before the administration of the vaccine. The data from each source were validated, managed, and de-identified by the Government Big Data Institute (GBDi). The Vaccine Safety and Data Monitoring Committee (VSDMC) was responsible for both COVID-19 vaccine safety management and the protection of personal data. Although the Thai Personal Data Protection Act (PDPA) was announced on May 27, 2019, but has been postponed to enforcement on June 1, 2022, this study has been carefully conducted in compliance with the Thai PDPA.

Study population

The study included all Thai individuals aged 12 years or older on the study start date and had received at least one dose of any COVID-19 vaccine at the CVC. Participants who did not have COVID-19 vaccine data were excluded. The study population was categorized into COVID-19 vaccine profiles defined based on the combination vaccine type and dosage they received for each dose. Participants were accounted for the latest dose after 7 days of vaccine administration to allow the antibodies to develop.[12,13] Participants were followed until the first of death or the end of the study period (January 31, 2022) whichever came first.

Statistical analysis

Categorical demographic data were presented as counts and percentages and continuous data were presented as mean and standard deviation along with median and interquartile ranges. The crude COVID-19 breakthrough infection, hospitalization rates, and mortality rates were calculated among vaccine profiles. We explored the marginal benefit of each shot of the COVID-19 vaccine ('shot effect') using time-to-event outcomes including breakthrough infection, hospitalization, and mortality with survival analysis. The association between the number of vaccination dose regardless of vaccination type and the primary outcomes were first evaluated using univariable Cox proportional hazard regression and subsequently adjusted for age and gender. The assumption of proportional hazards was verified using Schoenfeld residuals. Subgroup analyses were conducted with stratification on the month of infection to avoid variant

bias. Sensitivity analysis using logistic regression was conducted to evaluate the breakthrough infection outcome as a binary outcome. STATA, version 15.1 (College Station, TX), was used for all analyses. p values less than 0.05 were considered statistically significant.

Results

Characteristics of the participants

There were 2,407,315 eligible participants (mean age 42.84 ± 16.37 years old, 54.20% female) who received at least one COVID-19 vaccine at CVC, accounting for a total of 4,321,314 vaccine doses administered (Table 1). 12.69% were elderly aged more than 60 years, 8.81% had comorbidities, 0.41% were healthcare workers, 0.26% were village health volunteers, 0.20% were students, 0.18% were military officers, and 0.02% were police. There were 564 participants who received the first dose of COVID-19 vaccine from another healthcare provider prior centralized vaccination rollout at the CVC on May 24, 2021, and then received subsequent doses at the CVC. Among all participants, there were 63,469 (2.75%) breakthrough COVID-19 infections and 42,001 (1.74%) participants were hospitalized with a median length of stay of 12 days (IQR 9–14). The mortality rate was 0.02% with 436 participants dying from COVID-19 (Table 1).

Variable	n (%)
Doses	4,321,314
Participants	2,407,315 (100)
Female	1,304,871 (54.20)
Age	
Mean ± SD	42.84 ± 16.37
Median (IQR)	41 (30–54)
Primary Eligibility Categories	2,407,315
General	1,863,098 (77.39)
Elderly >60 years	305,402 (12.69)
Comorbidities	212,003 (8.81)
Students	4909 (0.20)
Pregnant Woman	798 (0.03)
Healthcare Workers	9850 (0.41)
Village Health Volunteers	6338 (0.26)
Non-Healthcare Workers	
Police	509 (0.02)
Soldier	4408 (0.18)
Infection	63,469 (2.75)
June 2021	1881 (0.03)
July 2021	7196 (0.11)
August 2021	16,115 (0.25)
September 2021	8039 (0.13)
October 2021	4090 (0.06)
November 2021	2646 (0.04)
December 2021	2398 (0.04)
January 2022	21,104 (0.33)
Admission	42,001 (1.74)
Length of Stay (Mean ± SD)	14.41 ± 16.31
Length of Stay (Median (IQR)	12 (9–14)
Death	436 (0.02)

Table 1: **Characteristics of the participants.**

COVID-19 vaccination profiles

There were 32 different COVID-19 vaccination profiles among participants (Fig. 1 and Supplementary Table S1). Most participants were vaccinated with two doses of VV (21.40%), followed by one dose of MR (20.68%), one dose of VV (19.70%), two doses of VV with one dose of MR as a third dose (14.31%), heterologous one dose of VV and one dose of MR as second dose (6.46%), heterologous one dose of IN and one dose of VV as second dose (4.74%), two doses of IN with one dose of VV as third dose (4.49%), two doses of MR (4.25%), two doses of IN (1.24%), and the remaining 23 COVID-19 vaccination profiles with less than 1% participants. Fig. 1 quantitatively visualizes the number of individuals who received each of the COVID-19 vaccines as their first, second, third, and fourth shots, representing both the homologous and heterologous vaccinations.

'Shot' and 'homologous' effects

Table 2 reported the number of participants who was at a specific vaccination profile at any specific time point. Potential shot and homologous effects for both prevention of breakthrough infection and hospitalization were observed—the participants with one-shot vaccination were the most infected with SARS-CoV-2 at 2.75%, followed by homologous two-shot at 1.91%, heterologous two-shot at 1.25%, and three-shot at 0.80%. Likewise, the participant with one-shot vaccination was the most hospitalized with COVID-19 at 1.79%, followed by homologous two-shot at 1.22%, heterologous two-shot at 0.66%, and three-shot at 0.44%.

Among one-shot vaccination profiles, participants with one dose of MR had the least COVID-19 infection at 0.76%, followed by one dose of VV at 3.34%, and one dose of IN at 3.61%. While the overall one-shot vaccination profile had the highest proportion of infected participants, the participants who received IN-IN had the highest proportion of COVID-19 breakthrough infection at 4.91% and VV-VV also had a high proportion at 1.51% while MR-MR showed a higher protective effect against COVID-19 infection (0.86%). However, there was no shot effect observed for MR-MR compared to MR for breakthrough infection. The two-shot heterologous vaccination profiles showed a better protective effect against COVID-19 breakthrough infection compared to their homologous counterparts (1.25% vs. 1.91%). Most three-shot vaccination profiles provided

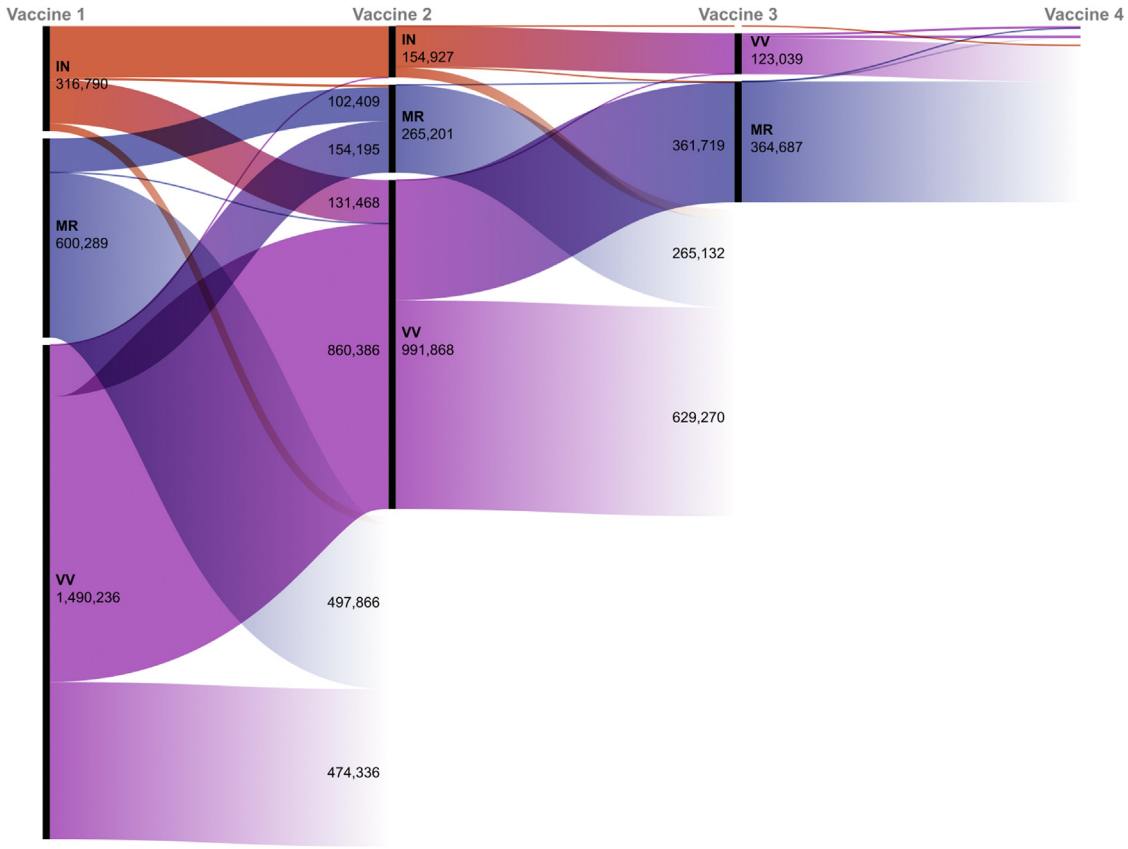

Fig. 1: **COVID-19 Vaccination Profiles**. Distributions of COVID-19 vaccines as the first, second, third, and fourth shots in Thai individuals—VV, ChAdOx1 nCoV-19; MR; mRNA-1273 or BNT162b2; IN, CoronaVac or BBIBP-CorV. The colors represent the vaccines—VV, purple; MR, blue; IN, orange—at each shot. The numbers represent frequency count of each vaccine at each shot. The change of color gradient reflects the change of vaccines between the doses.

the shot effect, but participants who received one shot of VV followed by two shots of MR demonstrated lower protection against COVID-19 (2.08%) compared to participants who received one shot of VV followed by one shot of MR (1.11%).

For protective effect against COVID-19 hospitalization among one-shot vaccination profile, participants with one dose of MR had the least COVID-19 hospitalization at 0.45%, followed by one dose of IN at 2.20%, and one dose of VV at 2.25%. While the overall one-shot vaccination profile showed the highest proportion of COVID-19 hospitalization, the participants who received two doses of IN had the highest proportion of COVID-19 hospitalization at 3.04% while the other homologous and heterologous two-shot vaccination profiles had less than 1% hospitalization. The homologous effect was observed for hospitalization as there was higher COVID-19 hospitalization in participants with two-shot homologous vaccination (1.22%) compared to those in participants with two-shot heterologous vaccination (0.66%). The participants with three-shot vaccination profiles showed similar COVID-19 hospitalization as their two-shot counterparts except for the participants who received one dose of VV followed by two doses of MR showed higher COVID-19 hospitalization at 1.96% compared to the participants who received one dose of AZ followed by one dose of PZ at 0.58%.

There was a potential shot effect observed when comparing one-shot to two-shot or more as the death rate of participants who had one-shot vaccine profiles was 0.02% while those who had two-shot vaccine profiles had less than 0.01% mortality and none of the participants who received three-shot vaccination died from COVID-19. However, the absolute number was small and the observed difference was negligible for death outcome.

Among participants who received one-shot vaccination, participants who received one-shot of VV had the highest death rate at 0.03% while MR and IN had less than 0.01% death rate. For those who had two-shot vaccine profiles, there were only three profiles including VV-VV, IN-IN, and IN-VV that had death outcomes, yet only less than 0.01%. Nevertheless, the other two-shot and all three-shot vaccine profiles had zero death outcomes.

Vaccination profile	Date range		Total	Infection		Hospitalization		Death	
	Begin	End		Eligible	Infected	Eligible	Hospitalized	Eligible	Death
First-Shot			2,407,315	2,308,201	63,469 (2.75%)	2,344,417	42,001 (1.79%)	2,407,304	431 (0.02%)
VV[a]	26 March 2021	31 January 2022	1,490,236	1,447,770	48,402 (3.34%)	1,464,728	32,889 (2.25%)	1,490,231	418 (0.03%)
MR[a]	13 August 2021	31 January 2022	600,289	560,654	4244 (0.76%)	574,499	2395 (0.42%)	600,286	1 (<0.01%)
IN[a]	22 March 2021	30 January 2022	316,790	299,777	10,823 (3.61%)	305,190	6717 (2.20%)	316,787	12 (<0.01%)
Second-Shot Homologous			1,117,487	1,067,642	20,434 (1.91%)	1,093,559	13,345 (1.22%)	1,117,699	20 (<0.01%)
VV-VV[a]	17 May 2021	31 January 2022	860,386	834,023	12,621 (1.51%)	844,658	8207 (0.97%)	860,383	15 (<0.01%)
MR-MR[a]	10 September 2021	31 January 2022	102,409	90,486	779 (0.86)	94,093	427 (0.45%)	102,409	0 (0.00%)
IN-IN[a]	8 April 2021	21 January 2022	154,907	143,133	7034 (4.91%)	154,808	4711 (3.04%)	154,907	5 (<0.01%)
Second-Shot Heterologous			294,450	259,615	3252 (1.25%)	269,586	1784 (0.66%)	294,290	1 (<0.01%)
VV-MR[a]	13 August 2021	31 January 2022	155,494	134,939	1497 (1.11%)	141,042	811 (0.58%)	155,493	0 (0.00%)
VV-IN	28 June 2021	31 October 2021	20	19	0 (0.00%)	19	0 (0.00%)	20	0 (0.00%)
MR-VV	1 October 2021	30 January 2022	14	14	0 (0.00%)	14	0 (0.00%)	14	0 (0.00%)
IN-VV[a]	14 June 2021	30 January 2022	131,468	118,946	1665 (1.40%)	122,379	926 (0.76%)	131,465	1 (<0.01%)
IN-MR	1 October 2021	31 January 2022	7298	5697	90 (1.58%)	6132	47 (0.77%)	7298	0 (0.00%)
Third-Shot			473,651	471,189	3763 (0.80%)	478,496	2125 (0.44%)	487,726	0 (0.00%)
VV-VV-VV	18 September 2021	31 January 2022	738	728	3 (0.41%)	731	3 (0.41%)	738	0 (0.00%)
VV-VV-MR	23 October 2021	31 January 2022	344,580	334,020	1774 (0.53%)	338,614	973 (0.29%)	344,579	0 (0.00%)
VV-MR-MR	25 November 2021	31 January 2022	53	48	1 (2.08%)	51	1 (1.96%)	53	0 (0.00%)
VV-IN-MR	22 December 2021	16 January 2022	3	3	0 (0.00%)	3	0 (0.00%)	3	0 (0.00%)
VV-IN-VV	27 September 2021	11 November 2021	3	3	0 (0.00%)	3	0 (0.00%)	3	0 (0.00%)
MR-MR-MR	27 November 2021	31 January 2022	10	10	0 (0.00%)	10	0 (0.00%)	10	0 (0.00%)
IN-VV-VV	24 September 2021	31 January 2022	141	117	1 (0.85%)	123	1 (0.81%)	141	0 (0.00%)
IN-VV-MR	12 December 2021	31 January 2022	17,139	15,950	67 (0.42%)	16,238	32 (0.20%)	17,139	0 (0.00%)
IN-MR-MR	6 December 2021	23 January 2022	6	5	0 (0.00%)	5	0 (0.00%)	6	0 (0.00%)
IN-IN-VV	28 June 2021	30 January 2022	122,157	117,866	1895 (1.61%)	120,174	1105 (0.92%)	122,157	0 (0.00%)
IN-IN-MR	13 August 2021	31 January 2022	2896	2437	22 (0.90%)	2542	10 (0.39%)	2895	0 (0.00%)
IN-IN-IN	1 December 2021	7 December 2021	2	2	0 (0.00%)	2	0 (0.00%)	2	0 (0.00%)

Participants contributed to each vaccine shot they received. For example, participants with IN-IN-VV would contribute to First-Shot IN, Second-Shot Homologous IN-IN, and Third-Shot IN-IN-VV. [a]VV, ChAdOx1 nCoV-19; MR; mRNA-1273 or BNT162b2; IN, CoronaVac or BBIBP-CorV.

Table 2: **Breakthrough infection, hospitalization, and death after COVID-19 vaccinations.**

Five major two-shot COVID-19 vaccination profiles

Of 1,327,257 participants who completed at least two shots of vaccination, a total of 861,545 had two-shot COVID-19 vaccination profiles in which most of the participants had VV-VV vaccine profiles while the smallest number of participants received IN-IN (Supplementary Figs. S1 and S2). While the overall breakthrough infection rate was 1.79% among participants with two-shot vaccination profiles, IN-IN had the highest breakthrough infection rate (6.36%), followed by VV-VV (1.51%), IN-VV (1.40%), and VV-MR (1.11%). There was an increasing trend of breakthrough infection after two-shot COVID-19 vaccination over time. For the first two months of the study period, all infections were from participants who received IN-IN. The breakthrough infection was also dominated by the IN-IN vaccine profile in August 2021, and afterward. On the other hand, there was rising in breakthrough infection among participants who received VV-VV or IN-VV from September 2021 to December 2021. In the last month of follow-up, there was a huge breakthrough infection among all participants who had major two-shot vaccine profiles, especially participants who had at least one dose of VV (Table 3).

Of 471,189 participants who received at least three-shot COVID-19 vaccination, 457,654 had the three-shot vaccine profiles in which 3648 (0.80%) had breakthrough infection, and participants with IN-IN-VV were the most infected with 1.71% breakthrough infection, followed by VV-VV-MR at 0.53% and IN-VV-MR at 0.42%. During the first two months of follow-up, there was no breakthrough infection among participants who received three doses of vaccination. During August–October 2021, there was a breakthrough infection among participants who received IN-IN-VV, but none for other three-shot profiles. The number of breakthrough infections slightly decrease during November–December 2021 before a sharp rising in January 2022 when participants with VV-VV-MR were the most infected in number, but IN-IN-VV had the most breakthrough infection rate (Table 4).

Survival analysis using Cox regression showed the shot effect of vaccine profiles per incremental shot after the first dose. There was an 18% risk reduction for breakthrough infection per vaccination shot added, and a 25% risk reduction for COVID-19 hospitalization per vaccination shot added ($p < 0.001$). Similarly, there was a huge protective effect against COVID-19 death in participants who received a higher number of vaccine shots with a 96% risk reduction per vaccination shot added. Sensitivity analysis using logistic regression was consistent with the main analysis. There was an 14% risk reduction for breakthrough infection comparing participants who received two doses of COVID-19 vaccination with those with one dose. The risk reduction for breakthrough infection increased to 62% in participants with three doses vaccination compared to one dose, and there was a 55% lower breakthrough infection in participants who received third-shot booster compared to those with two doses vaccination (Table 5).

Discussion

This study is the first and largest prospective cohort that could compare the breakthrough infection, hospitalization, and death across multiple different COVID-19 vaccination profiles. Real-life data from a large-scale, government-mandated centralized COVID-19 mass vaccination program, merged with three validated national datasets, provided great opportunities to investigate several research questions regarding the COVID-19 vaccination rollout strategies.

Thirty-two different COVID-19 vaccination profiles revealed in this prospective cohort study allowed us to assess the marginal benefit of each shot of the COVID-19 vaccine ('shot effect') as well as the comparative

	Total	VV[a]-VV	MR[a]-MR	IN[a]-IN	VV-MR	IN-VV
Eligible	1,327,257	834,023	90,486	143,133	134,939	118,946
Infected	23,686 (1.78%)	12,621 (1.51%)	779 (0.86%)	7034 (4.91%)	1497 (1.11%)	1665 (1.40%)
Two-Shot only	861,545	498,047	90,476	29,594	134,890	102,819
Two-Shot only with infected	15,400 (1.79%)	9616 (1.93%)	779 (0.86%)	1883 (6.36%)	1495 (1.11%)	1537 (1.49%)
June 2021	37 (0.24%)	0 (0.00%)	0 (0.00%)	37 (100%)	0 (0.00%)	0 (0.00%)
July 2021	303 (1.97%)	0 (0.00%)	0 (0.00%)	303 (100%)	0 (0.00%)	0 (0.00%)
August 2021	569 (3.69%)	0 (0.00%)	0 (0.00%)	568 (99.82%)	0 (0.00%)	1 (0.18%)
September 2021	683 (4.44%)	194 (28.4%)	0 (0.00%)	440 (64.42%)	1 (0.15%)	48 (7.03%)
October 2021	875 (5.68%)	648 (74.06%)	0 (0.00%)	118 (13.49%)	2 (0.23%)	107 (12.23%)
November 2021	1102 (7.16%)	914 (82.94%)	6 (0.54%)	55 (4.99%)	1 (0.09%)	123 (11.16%)
December 2021	1278 (8.3%)	985 (77.07%)	27 (2.11%)	43 (3.36%)	79 (6.18%)	138 (10.8%)
January 2022	10,553 (68.53%)	6875 (65.15%)	746 (7.07%)	319 (3.02%)	1412 (13.38%)	1120 (10.61%)

[a]VV, ChAdOx1 nCoV-19; MR; mRNA-1273 or BNT162b2; IN, CoronaVac or BBIBP-CorV.

Table 3: **Breakthrough infection after two-shot COVID-19 vaccinations by months of infection.**

Variables	Total	VV[a]-VV-MR[a]	IN[a]-IN-VV	IN-VV-MR
Eligible	471,189	334,020	117,866	15,950
Infected	3763 (0.80%)	1774 (0.53%)	1895 (1.61%)	67 (0.42%)
Three-Shot only	457,654	334,015	104,532	15,950
Three-Shot only with infection	3648 (0.80%)	1774 (0.53%)	1785 (1.71%)	67 (0.42%)
June 2021	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
July 2021	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
August 2021	4 (0.11%)	0 (0.00%)	4 (100%)	0 (0.00%)
September 2021	9 (0.25%)	0 (0.00%)	9 (100%)	0 (0.00%)
October 2021	122 (3.34%)	0 (0.00%)	122 (100%)	0 (0.00%)
November 2021	106 (2.91%)	0 (0.00%)	105 (99.06%)	0 (0.00%)
December 2021	102 (2.8%)	8 (7.84%)	94 (92.16%)	0 (0.00%)
January 2022	3305 (90.6%)	1766 (53.43%)	1451 (43.9%)	67 (2.03%)

[a]VV, ChAdOx1 nCoV-19; MR; mRNA-1273 or BNT162b2; IN, CoronaVac or BBIBP-CorV.

Table 4: **Breakthrough infection after three-shot COVID-19 vaccinations by months.**

effectiveness between homologous and heterologous vaccinations ('homologous effect'). We found that the anticipated shot effect between participants who had one-shot and two-shot vaccination was not consistently observed. There was the lowest effectiveness of two doses of inactivated vaccine for COVID-19 infection which was not expected since there were several studies that demonstrated the shot effect of inactivated vaccine for overall COVID-19 infection,[14–16] and symptomatic COVID-19 infection.[17,18] Additionally, two shots of viral vector vaccine had a less protective effect against COVID-19 infection compared to one shot of mRNA vaccine, and there was no shot effect observed between one and two shots of mRNA vaccine which might relate to time from the last vaccination dose in which the vaccine effectiveness of two-shot MR was drastically declined.[19] The results were against the previous study on two doses of viral vector,[20,21] and two doses of mRNA vaccines.[22] For hospitalization outcomes, two doses of inactivated vaccine were underperformed compared to one dose of any vaccine which was unexpected since there were some evidence of higher benefit for COVID-19 hospitalization of two doses compared to one dose of CoronaVac.[14,17] The shot effect for hospitalization outcome was observed as expected. The rationale for no shot effect between one-shot and two-shot vaccine profiles might relate to the different study periods, inconsistent definitions of outcomes, different study designs, or unmeasured confounding factors. While met the proportional hazard assumption, we observed lower protective effect of second shot vaccination (two-shot compared to one-shot vaccine profiles) compared to third shot vaccination (three-shot compared to two-shot vaccine profiles).

There was a homologous effect observed in this study since homologous two-shot vaccine profiles showed higher COVID-19 infection and hospitalization compared to their heterologous two-shot vaccine

Variables	n	Univariable		Multivariable[a]	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Cox Proportional Hazard Regression					
Breakthrough Infection					
Per shot added after 1st dose	2,270,110	0.82 (0.81, 0.84)	<0.001	0.82 (0.80, 0.82)	<0.001
Hospitalization					
Per shot added after 1st dose	2,313,737	0.75 (0.74, 0.77)	<0.001	0.75 (0.73, 0.76)	<0.001
Death					
Per shot added after 1st dose	2,393,028	0.04 (0.03, 0.06)	<0.001	0.04 (0.03, 0.06)	<0.001
Logistic Regression					
Breakthrough Infection					
Two-Shot vs One-Shot	2,270,110	0.86 (0.84, 0.88)	<0.001	0.86 (0.84, 0.88)	<0.001
Three-Shot vs One-Shot	2,270,110	0.38 (0.37, 0.39)	<0.001	0.38 (0.37, 0.40)	<0.001
Three-Shot vs Two-Shot	2,270,110	0.44 (0.43, 0.46)	<0.001	0.45 (0.43, 0.46)	<0.001

[a]Adjusted by age and gender.

Table 5: **Multivariable regression of COVID-19 infection, hospitalization, and death after COVID-19 vaccinations.**

profiles. The homologous effect for COVID-19 infection was consistent with the previous studies on the homologous inactivated vaccine,[16] and viral vector vaccine.[23] In addition, the homologous effect was observed on the death outcome in this study. The homologous effect could be explained by the potentially lower immunogenicity of homologous two-shot vaccine profiles. A cohort study on the immunogenicity of homologous and heterologous inactivated and adenovirus vector vaccines demonstrated lower immunoglobulin G (IgG) and neutralizing antibodies produced by homologous inactivated vaccines compared to heterologous counterparts.[24] Similarly, there were several studies providing evidence of homologous effect with lower IgG, neutralizing antibody, and cellular immunity produced by homologous two-shot viral vector vaccine compared to the heterologous viral vector plus mRNA vaccine.[25–28] The homologous effect was also consistent with a recent case–control study from Thailand.[29]

We were unable to directly compare the effectiveness in preventing breakthrough infection across the vaccination profiles because they were introduced at different time points whereas the infection could be from different COVID-19 variants. To alleviate this 'variant bias', we performed an analysis by months of infection, presumably representing the most common variant for the specific month. The first surge of COVID-19 breakthrough infection in this cohort was during July 2021 which was the period the Delta variant was predominated in Thailand. During July to September 2021, most cases were from participants with IN-IN profiles which could be either from the low effectiveness against Delta variant of IN vaccine itself or due to the fact that IN-IN vaccine profile was implemented earlier than another Two-Shot vaccine profile and the antibody against SARS-CoV-2 might wean out as we could observe the rising of breakthrough infection from Delta variant in participants with VV-VV and IN-VV vaccine profile started from September 2021. It was also noteworthy that there was no breakthrough infection from participants with MR-MR vaccine profile until November 2021 which might occur due to the late implementation of MR-MR which started in October 2021. The Omicron variant hit Thailand during late December and became dominant variant during January 2022 in which we observed dramatic rising in breakthrough infection in this study. While VV-VV had better overall effectiveness against SARS-CoV-2 than IN-IN vaccine profile, it was interesting that there was a slightly higher breakthrough infection in VV-VV group compared to IN-IN during Omicron surge in Thailand.

The result comparing IN-IN and IN-IN with either VV or MR as third dose showed the similar result with small-scale studies on immunogenicity. There was evidence on higher immunogenicity for both IgG and neutralizing antibody in participants who received IN-IN-VV compared to IN-IN.[30] Similarly, the study on IN-IN-MR demonstrated higher humoral immunity compared to IN-IN.[31] While VV as the third dose after IN-IN showed promising result on real world data,[32] the randomized controlled trial showed superior humoral immunogenicity for both IgG and neutralizing antibody for IN-IN-MR compared to IN-IN-VV.[33] The conclusion for the need of third dose for population who received two doses of IN was consistent with the need of a third booster dose provided by an earlier study.[34] There was an unusual observation that 1 shot of VV followed by 2 shots of MR had lower protection than 1 shot of VV followed by 1 shot of MR. This phenomenon should be interpreted with caution and might be explained by the small number of participants who received 1 shot of VV followed by 2 shots of MR which might overestimate the outcome if occurred.

This study has several strengths. First, a large amount of individual-level data on both the COVID-19 vaccination and the final clinical outcomes rather than measuring immunogenicity. Second, the vaccine-seeking behavior in real-world setting could be reflected by the vaccination profiles. Thirds, the effects of the number of shots and types of vaccine could be investigated. Nonetheless, some limitations should be noted for this real-life prospective observational study. First, some COVID-19 vaccines were not available in Thailand so there were not included in the analyses. Second, there was the inclusion of rapid antigen test as one of diagnostic tool for COVID-19 infection in Co-Lab system since August 11, 2021 which might underestimate the breakthrough infection as the rapid antigen test was less sensitive compared to real-time RT-PCR. On the other hands, considered real-time RT-PCR testing capacity in Thailand during the study period, introduction of rapid antigen test might overestimate the breakthrough infection as rapid antigen test had less specificity than real-time RT-PCR while drastically increased the daily testing capacity. Third, there was a limitation on the information on comorbidity in this study due to the usage of real-world data. Fourth, some vaccine profiles had only small number of participants which might overestimate the outcome if the outcome occurred. Finally, the number of participants with four-shot vaccine profiles was limited, thus preventing further analysis. A study focusing on the fourth shot booster is needed to assess the optimal vaccine profiles and vaccination interval.

Breakthrough infection, hospitalization, and death from COVID-19 could differ across vaccination profiles that have a different number of shots and types of vaccine.

Contributors

M.W., T.N., and K.P. conceptualized and designed the study. M.W. and K.S. were involved with patient management and sample collection. M.W., K.S., P.Phu., P.R., D.W., P.N.P., and N.C. were involved with data

collection and data entry. T.N., K.S., P.Phu., and P.Pun., were responsible for digitalization of records and statistical analysis. M.W. and K.P. were responsible for project oversight. M.W., T.N., and K.P. drafted the manuscript. P.R. prepared the infographics. All authors had access to the data, critically reviewed the study for intellectual content, and had full responsibility for the final manuscript.

Data sharing statement

The CVC Registry, Co-Lab, CO–Ward, and Death Registry were obtained from several Thai governmental agencies and protected under the Thai Personal Data Protection Act B.E. 2019 as well as the Memorandum of Understanding between 12 Thai governmental agencies signed on March 17, 2022. A reasonable request could be submitted to be considered by the Vaccine Safety and Data Monitoring Committee (VSDMC).

Declaration of competing interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2022.100106.

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