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Short-term immune response after inactivated SARS-CoV-2 (CoronaVac®, Sinovac) and ChAdOx1 nCoV-19 (Vaxzevria®, Oxford-AstraZeneca) vaccinations in health care workers

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Abstract

Background: Inactivated SARS-CoV-2 (CoronaVac®, Sinovac, or SV) and ChAdOx1 nCoV-19 (Vaxzevria®, Oxford-Astra Zeneca, or AZ) vaccines have been administered to the health care workers (HCWs).

Objective: To determine the short-term immune response after the SV and AZ vaccinations in HCWs.

Methods: In this prospective cohort study, HCWs who completed a 2-dose regimen of the SV or AZ were included. Immune response was evaluated by surrogate viral neutralization test (sVNT) and anti-SARS-CoV-2 total antibody. Blood samples were analyzed at 4 and 12 weeks after the complete vaccination. The primary outcome was the seroconversion rate at 4-weeks after complete immunization.

Results: Overall, 185 HCWs with a median (IQR) age of 40.5 (30.3-55.8) years (94 HCWs in the SV group and 91 in the AZ group) were included. At 4 weeks after completing the SV vaccination, 60.6% (95%CI: 50.0-70.6%) had seroconversion evaluated by sVNT (≥ 68% inhibition), comparable to the patients recovered from mild COVID-19 infection (69.0%), with a rapid reduction to 12.2% (95%CI: 6.3-20.8) at 12 weeks. In contrast, 85.7% (95%CI: 76.8-92.2%) HCWs who completed two doses of the AZ for 4 weeks had seroconversion, comparable to the COVID-19 pneumonia patients (92.5%), with a reduction to 39.2% (95%CI: 28.4-50.9%) at 12 weeks. When using the anti-SARS-CoV-2 total antibody level (≥ 132 U/ml) criteria, only 71.3% HCWs in the SV group had seroconversion, compared to 100% in the AZ group at 4 weeks.

Conclusion: A rapid decline of short-term immune response in the HCWs after the SV vaccination indicates the need for a vaccine booster, particularly during the ongoing spreading of the SARS-CoV-2 variants of concern.

Key words: SARS-CoV-2 vaccine, COVID-19 vaccine, Surrogate viral neutralizing antibody titer, Anti-SARS-CoV-2 total antibody, Health care workers, Inactivated SARS-CoV-2 vaccine

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Introduction

With efforts to create immunity against the global spreading of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or Coronavirus diseases 2019 (COVID-19), several SARS-CoV-2 vaccines have been developed and widely distributed. In Thailand, inactivated SARS-CoV-2 (CoronaVac®, Sinovac, or SV) and ChAdOx1 nCoV-19 (Vaxzevria®, Oxford-AstraZeneca, or AZ) vaccines have been administered to the front-line health care workers (HCWs) since March 2021. While the SV is an inactivated whole-virion SARS-CoV-2 vaccine, the AZ is a replication-deficient adenoviral vector vaccine.[1,2] Therefore, the immunological mechanisms of vaccine-induced protection against SARS-CoV-2 in humans were different.[3] The inactivated SARS-CoV2 vaccine mainly activates B-cell response whereas the viral vector vaccine activates both B-cell and T-cell response.

In general, natural infection creates a protective immunity against re-infection. However, in the COVID-19 patients, the re-infection is possible, whereas the definitive antibody level for protective immunity remains inconclusive.[4,5] Moreover, recent evidence suggests that a high neutralizing titer may be required for protection against the circulating SAR-CoV-2 variants of concern (VOCs) infection and symptomatic disease.[6,7] To measure the SARS-CoV-2 vaccine-induced protective immune response against the symptomatic infection, the neutralizing antibody titer against the SARS-CoV-2 is a highly predictive indicator. The gold standard for neutralizing antibody detection is a plaque reduction neutralizing test ($PRNT_{50}$), which requires live pathogen and complex laboratory settings. Therefore, the more simplified technique using surrogate virus neutralization test (sVNT), which detects total immunodominant neutralizing antibodies targeting the viral spike (S) protein receptor-binding domain (RBD), is generally used as a high sensitivity and specificity rapid test.[8] Additionally, the binding antibody (total antibodies including IgG, IgM, and IgA) against the SARS-CoV-2 can be detected with simple laboratory techniques, including rapid test, Enzyme-Linked Immunosorbent Assay (ELISA), and Electrochemiluminescence Assay.

Our study, therefore, aimed to determine the immune response after the SV and AZ vaccination in the HCWs, in comparison with the patients recovered from the COVID-19 using sVNT (% inhibition) and anti-SARS-CoV-2 total antibodies (U/ml). Moreover, the correlation between the sVNT and anti-SARS-CoV-2 total antibodies for estimating vaccine efficacy against SARS-CoV-2 was evaluated.

Methods

The prospective cohort study included HCWs who received the SARS-CoV2 vaccination at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The study was approved by the Research Ethics Review Committee, Faculty of Medicine, Chulalongkorn University, and was registered to the Thai Clinical Trial (TCTR20210325003). The protocol was performed in accordance with the declaration of Helsinki and its later amendments. All participants were voluntary to receiving the SARS-CoV-2 vaccination and participating in the study with written informed consent.

Study Population

Inclusion criteria were as follows: (1) HCWs aged 18 years old and above; and (2) no history of the COVID-19. HCWs who had (1) ongoing immunosuppressive medications; (2) any vaccinations within 1 month; or (3) any blood components or intravenous immunoglobulin administrations within 3 months; were excluded. In this study, all HCWs selected the type of vaccines based on their preference and the availability of the vaccine during the enrolment. Overall, each vaccination group consisted of 50 participants aged 18-40 years and 50 aged 41-70 years. In the SV group, 0.5 ml (3 μg) of inactivated SARS-CoV-2 (CoronaVac®, Sinovac, or SV) vaccine was administered intramuscularly at the deltoid region, using a 2-dose regimen with an interval of 21-28 days. For the ChAdOx1 nCoV-19 (Vaxzevria®, Oxford-AstraZeneca, or AZ) vaccination group, 0.5 ml of the AZ containing 5×10^{10} viral particles was administered intramuscularly at the deltoid region, using a 2-dose regimen with an interval of 8-10 weeks.

For the COVID-19 group, data were collected from patients diagnosed with the SARS-CoV-2 infection at the Emerging Infectious Diseases Clinical Center at King Chulalongkorn Memorial hospital from March to April 2020, which, at that time, the wild-type SARS-CoV-2 was the main circulating strain in Thailand. The COVID-19 was diagnosed by reverse transcriptase-polymerase chain reaction (RT-PCR) of SARS-CoV-2 from the throat and nasopharyngeal swab samples. The COVID-19 patients were classified according to the clinical severity into mild COVID-19 and COVID-19 pneumonia. Mild COVID-19 was defined as having either asymptomatic infection or upper respiratory tract infection. The COVID-19 pneumonia was defined as having clinical features that vary in severity from requiring no oxygen supplement to the mechanical ventilator. Of note, all COVID-19 pneumonia cases were received antiviral medications.

Demographics and Clinical Data

Baseline demographics and clinical data, including medical history, current medications used, a history of exposure to the COVID-19 patients and a history of SARS-CoV2 infection, were collected. All HCWs were highly aware of their infection risk. Moreover, they had to follow the surveillance protocol, including a daily questionnaire to screen for the COVID-19 symptoms and exposure risk. Any HCWs with the presence of any symptoms or risk factors were tested for the SARS-CoV2 infection using the RT-PCR technique. In addition, for the COVID-19 patients, the clinical characteristics of the SARS-CoV-2 infections were evaluated.

Sample Collections and Study Protocol

For the vaccination groups, 4-ml clotted blood was collected at baseline for all participants, then at 4 and 12 weeks (+/-2 weeks) after completing 2-dose of the SV and the AZ vaccination and at 4 weeks (+/-2 weeks) after the first dose of the AZ vaccination.

For the COVID-19 group, the blood samples were collected at the time of diagnosis, 4 (+/-2) and 12 (+/-2) weeks after diagnosis.

The Detection of Antibody Titers Against SARS-CoV-2

The antibody titers against SARS-CoV-2 were determined by the surrogate neutralizing antibody and total antibodies using the ELISA technique.

1. The SARS-CoV-2 Neutralizing Antibody

The SARS-CoV-2 neutralizing antibody was detected by the blocking ELISA technique of the cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript), which the US Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs). The protein-protein interaction between Horseradish peroxidase (HRP) conjugated recombinant SARS-CoV-2 RBD fragment (HRP-RBD), and the human ACE2 receptor protein (hACE2) can be blocked by neutralizing antibodies against SARS-CoV-2 RBD. The neutralizing antibody level was detected as percent signal inhibition (% inhibition) following the manufacturer's protocol. Briefly, serum (negative or positive controls) was diluted 10-fold in a sample diluent (as described in the package insert), mixed with HRP-RBD, then incubated at 37°C for 30 minutes. After incubation, the mixture was added to the hACE2-coated well and incubated at 37°C for 30 minutes. The ELISA plate was then washed with a wash solution for 4 times. The 3,3′,5,5′-tetramethylbenzidine (TMB) substrate was added and incubated for 15 minutes. Finally, the stop solution was added before the optical density (OD) value at 450 nm was read. The antibody level is described as the percentage of signal inhibition or % inhibition.[8] The percent signal inhibition was calculated using the equation from the manufacturer with the cut-off level for SARS-CoV-2 neutralizing antibody detection of ≥ 30% inhibition.

$$\text{Percent signal inhibition} = 1 - \left(\frac{\text{OD}_{\text{value of sample}}}{\text{OD}_{\text{value of negative control}}}\right) \times 100\%$$

The seroconversion rate was defined as sVNT ≥ 68%, adopted from the US-FDA guidance of a high titer of the COVID-19 convalescent plasma.[9]

2. The SARS-CoV-2 Total Antibodies

The SARS-CoV-2 total antibodies were detected by the Elecsys® Anti-SARS-CoV-2 S using Cobas e411 immunoassay analyzers (Roche Diagnostics, Rotkreuz, Switzerland), which is also the US-FDA EUAs. The Elecsys® is the immunoassay for SARS-CoV-2 total antibodies against the RBD of the S antigen detection, and the antibody level is reported as U/ml. Two hundred microliter of serum sample was used following the manufacturer's protocol. The criteria of negative for SARS-CoV-2 total antibodies is < 0.8 U/ml. For the participants who had the SARS-CoV-2 total antibodies over the maximum measuring range (which is > 250 U/ml), 10-fold diluted samples using the Elecsys® Diluent Universal were re-evaluated.[10] The seroconversion rate was defined as the anti-SARS-CoV-2 total antibodies ≥ 132 U/ml as suggested by the US-FDA of the high titer for COVID-19 convalescent plasma.[9]

The level of anti-SARS-CoV-2 total antibodies (measured in U/ml) from the Elecsys® test was converted to the BAU/ml following the first WHO International Standard for anti-SARS-CoV-2 immunoglobulin, which 1 U/ml is equivalent to 0.972 BAU/ml.[11]

Statistical Analysis

Demographics and clinical and laboratory parameters were described in descriptive statistics. Continuous variables were presented as median and interquartile range (IQR). The Wilcoxon rank-sum test was applied to compare the continuous variables between two groups and the Kruskal-Wallis test in case of more than two groups. The Chi-square test or Fisher exact test were used to compare the proportion between groups. The correlation between sVNT and anti-SARS-CoV-2 total antibodies was determined by the Spearman rank test. Statistical significance was considered as $P < 0.05$. STATA version 15.1 (Stata Corp., College Station, Texas) was used for statistical analysis.

Results

For the vaccination groups, a total of 200 HCWs participated in the study. However, only 185 participants completed the 2-dose regimen of the vaccinations and had the blood collection at 4 weeks after the second dose (94 and 91 participants in the SV and the AZ groups, respectively). The median (IQR) intervals between the second dose and the blood collection were 23 (22-24) days for the SV group and 19 (16-21) days for the AZ group. For the COVID-19 group, a total of 182 COVID-19 patients were admitted to King Chulalongkorn Memorial Hospital during March and April 2020. One hundred eleven patients had convalescent sera collected at approximately 1 month after diagnosis with a median (IQR) interval of 35 (30-38) days. Of 111 patients, 58 were diagnosed with mild COVID-19 (including upper respiratory tract infection (URI)) and 53 with COVID-19 pneumonia (including 26 moderate (who required no oxygen supplement) and 23 severe pneumonia (who required oxygen supplement or ventilator support) patients). Demographic data and clinical characteristics are described in **Table 1**. The HCWs included physicians, nurses and nurse assistants. As high as 52.1% of participants in SV group had been involved in the COVID-19 service, for example, out-patient clinic, in-patient clinic, emergency department or delivery room, compared to the 15.4% of participants in AZ group. One-third of participants had underlying medical conditions, which commonly were hypertension and dyslipidemia,

Table 1. Demographics data of health care workers who received inactivated SARS-CoV-2 vaccine (CoronaVac®, Sinovac, or SV) and ChAdOx1 nCoV-19 vaccine (Vaxzevria®, Oxford-AstraZeneca, or AZ) or patients with COVID-19 diseases

	Inactivated SARS-CoV2 (SV) (N = 94)	ChAdOx1 nCoV-19 (AZ) (N = 91)	All COVID-19 disease (N = 111)	COVID-19		*P*-value
				mild COVID-19 (N = 58)	COVID-19 pneumonia (N = 53)	
Age, year, median (IQR)	40.8 (30.8-51.4)	40.4 (29.6-60.4)	36 (27-47)	31 (26-38)	43 (32.5-50.5)	0.001[a]
Age group, n (%)						< 0.001[b]
20-30 year	26 (27.7)	30 (33)	40 (36)	28 (48.3)	12 (22.6)	
31-50 year	44 (46.8)	19 (20.9)	54 (48.7)	27 (46.7)	27 (50.9)	
51-70 year	24 (25.5)	42 (46.2)	17 (15.3)	3 (5.2)	14 (26.4)	
Female, n (%)	76 (80.9)	68 (72.3)	67 (60.4)	37 (63.8)	30 (57.7)	0.005[b]
BMI (kg/m^2), median (IQR)	22 (20.1-25.6)	22.8 (20.3-25.6)	22.5 (19.5-26.7)*	20.8 (18.8-23.2)	23.4 (19.8-27.1)	0.45[a]
Interval between vaccine completion or COVID-19 diagnosis and the blood collection, day, median (IQR)	23 (22-24)	19 (16-21)	35 (30-38)	34 (30-38)	35 (31-39)	NA

*N = 55
[a] indicates *P*-value from Kruskal-Wallis test and [b] from Chi-square test
Abbreviations: IQR = interquartile range

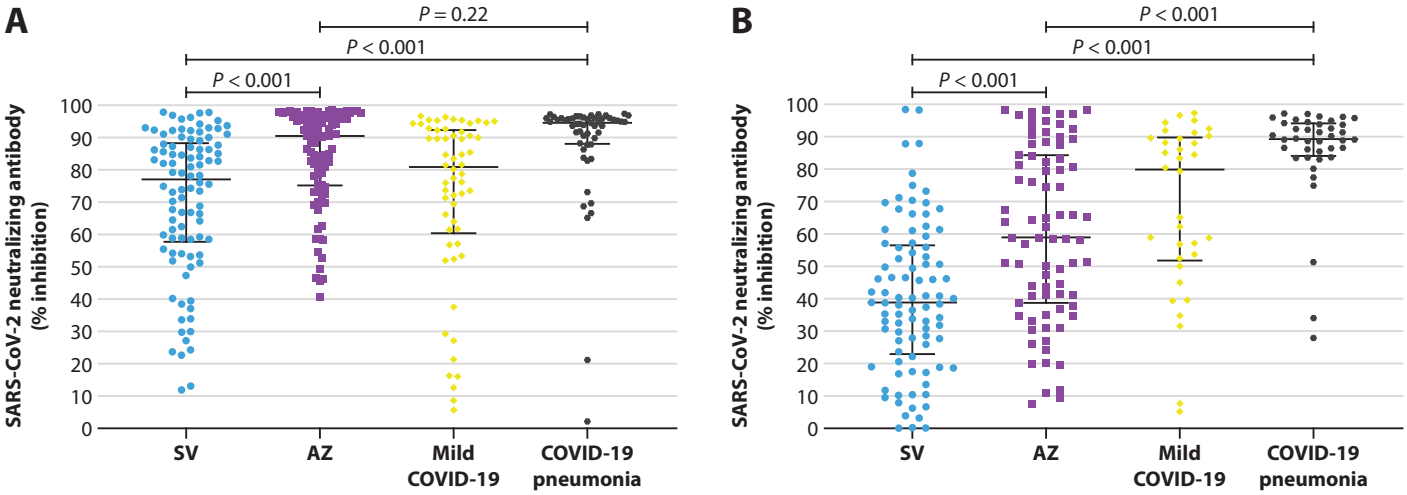

Figure 1. The SARS-CoV-2 Neutralizing antibody using the cPass™ test (% inhibition) at 4 weeks (A) and 12 weeks (B) after complete 2-dose of inactivated SARS-CoV-2 vaccine (CoronaVac®, Sinovac, or SV) and ChAdOx1 nCoV-19 vaccine (Vaxzevria®, Oxford-AstraZeneca, or AZ) compare to convalescent sera after COVID-19 diseases

and there was no significant difference between two group. At baseline, the immune response of all participants in the vaccination groups was confirmed to be negative by both tests.

The SARS-CoV-2 Neutralizing Antibodies (sVNT, % inhibition)

The sVNTs (% inhibition) at 4 and 12 weeks after completing the second dose of the vaccinations are demonstrated in **Figure 1**, **Table 2**. The median (IQR) of SARS-CoV-2 sVNT was 77.0 (58.5-87.9) % inhibition in the SV group, 90.4 (75.2-96.2) % inhibition in the AZ group at 4-week after complete vaccination, 80.8 (61.5-92.1) % inhibition in the mild COVID-19 group, and 94.5 (88.1-95.8) % inhibition in the COVID-19 pneumonia group at 4-week after diagnosis.

For the SV group, sVNT tended to be lower in the older age group but was not statistically significant (83.2% inhibition in the 20-30 years group vs 73.4% inhibition in the 51-60 years group, P = 0.18). There was no statistically significant difference of sVNT between age ranges and sexes in each group. (**Table 2**) Comparing to the convalescent sera of the COVID-19 patients, the SV group had a level of SARS-CoV-2 neutralizing antibodies comparable to the mild COVID-19 group. In contrast, the AZ group had a higher level of neutralizing antibodies comparable to the COVID-19 pneumonia group at 4-week after completing immunization. (**Figure 1A**)

Table 2. Median (IQR) of the SARS-CoV2 Neutralizing antibody using the cPass™ test and the anti-SARS-CoV-2 total antibody using the Elecsys™ test at 4 weeks after complete 2-dose of inactivated SARS-CoV-2 vaccine (CoronaVac®, Sinovac, or SV) and ChAdOx1 nCoV-19 vaccine (Vaxzevria®, Oxford-AstraZeneca, or AZ) compare to convalescent sera after 4-week COVID-19 disease

Median (IQR)	SARS-CoV2 Neutralizing antibody (% inhibition)					Anti-SARS-CoV-2 total antibody (U/mL)				
	Inactivated SARS-CoV2 (SV) (N = 94)	ChAdOx1 nCoV-19 (AZ) (N = 91)	mild COVID-19 (N = 58)	COVID-19 pneumonia (N = 53)	*P*-value[a]	Inactivated SARS-CoV2 (SV) (N = 94)	ChAdOx1 nCoV-19 (AZ) (N = 91)	mild COVID-19 (N = 58)	COVID-19 pneumonia (N = 53)	*P*-value[a]
Overall	77.0 (58.5-87.9)	90.4 (75.2-96.2)	80.8 (61.5-92.1)	94.5 (88.1-95.8)	< 0.001	188.6 (115.6-312.2)	794.2 (497.9-1383.0)	66.9 (19.7-170.2)	241.3 (170.3-442.9)	< 0.001
Age, year										
20-30	83.2 (59.0-92.7)	88.2 (78.1-95.9)	74.7 (52.9-89.9)	91 (76.2-94.5)	0.03	275.8 (101.1-580.2)	583.1 (459.7-864.7)	49.2 (14.9-119.9)	183.1 (81-244.2)	< 0.001
31-50	77.3 (59.1-87.5)	95.6 (75.6-97.9)	89.5 (64-94.3)	94.7 (89.8-95.7)	< 0.001	187.6 (115.6-282.3)	933.6 (516.2-1949)	125.9 (18.1-192.1)	241.3 (181.1-495.8)	< 0.001
51-70	73.4 (49.3-83.2)	90.2 (72.5-95.6)	84.7 (71.3-92.1)	95.7 (93.8-96.8)	< 0.001	185.6 (129.9-286.3)	841.2 (497.9-1657)	39.9 (21.9-226.1)	376.8 (207.9-936.4)	0.001
P-value[a]	0.11	0.27	0.39	0.04		0.22	0.09	0.32	0.04	
Sex										
Male	67.9 (58.5-86.2)	85.4 (74.0-93.8)	71.3 (53.5-89.4)	95.3 (91.8-96.1)	< 0.001	180.1 (101.1-227.1)	735.4 (447.6-886.4)	40.8 (5.42-108.7)	411.1 (241.3-866.9)	< 0.001
Female	78.6 (57.0-88.5)	91.1 (75.2-96.9)	84.6 (72.1-92.7)	93.8 (87.7-95.6)	< 0.001	222.5 (120.5-339.1)	834.1 (506.9-1506)	107.5 (21.8-192.1)	208.1 (142.7-354.6)	< 0.001
P-value[b]	0.59	0.16	0.10	0.13		0.42	0.18	0.15	0.01	

[a] indicates *P*-value from Kruskal-Wallis test and [b] from Wilcoxon rank sum test

At 12-week after the second dose of the SV vaccination, the median (IQR) of SARS-CoV-2 sVNT decreased to 38.7 (22.1-55.7) % inhibition, which significantly decreased from the immune response at 4 weeks (77.0 (58.5-87.9) % inhibition) ($P < 0.001$). (**Figure 2A**) On the contrary, the median (IQR) of SARS-CoV-2 sVNT at 4 weeks after the first dose of AZ was 37.6 (6.5-63.2) % inhibition and significantly increased after 4 weeks of the second dose to 90.4 (75.2-96.2) % inhibition ($P < 0.001$). At 12-week after completing the vaccination, the median (IQR) of SARS-CoV-2 sVNT decreased to 58.8 (38.6-84.2) % inhibition in the AZ group. However, sVNT in COVID-19 group still remained at a high level; 79.8 (52.3-89.5) % inhibition in the mild COVID-19 group, and 89.2 (84.4-93.9) % inhibition in the COVID-19 pneumonia group. For the US-FDA guidance of a high titer of the COVID-19 convalescent plasma, the % inhibition using the cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit should be 68% and over (or ≥ 68% inhibition). At 4 weeks after completing the vaccinations, 57/94 (60.6%) participants in the SV group had ≥ 68% inhibition, compared to 78/91 (85.7%) participants in the AZ group. (**Table 3**) However, only 11/90 (12.2%) participants in the SV group had the high titers at 12 weeks after the second dose. For the AZ group, 17/87 (19.5%) participants had ≥ 68% inhibition at 4 weeks after the first dose, 78/87 (85.7%) and 31/79 (39.2%) at 4- and 12- week after the second dose, respectively

For sensitivity analysis, a higher cPass™ SARS-CoV-2 Neutralization Antibody Detection Assays of ≥ 80% inhibition was used as a surrogate marker for high sVNT against the SARS-CoV-2 VOC. Consequently, only 43/94 (45.7%) participants in the SV group and 64/91 (70.3%) participants in the AZ group had ≥ 80% inhibition, compared to 46/53 (86.8%) patients in the COVID-19 pneumonia group ($P < 0.001$) at 4-week after completing vaccination. (**Table 3**)

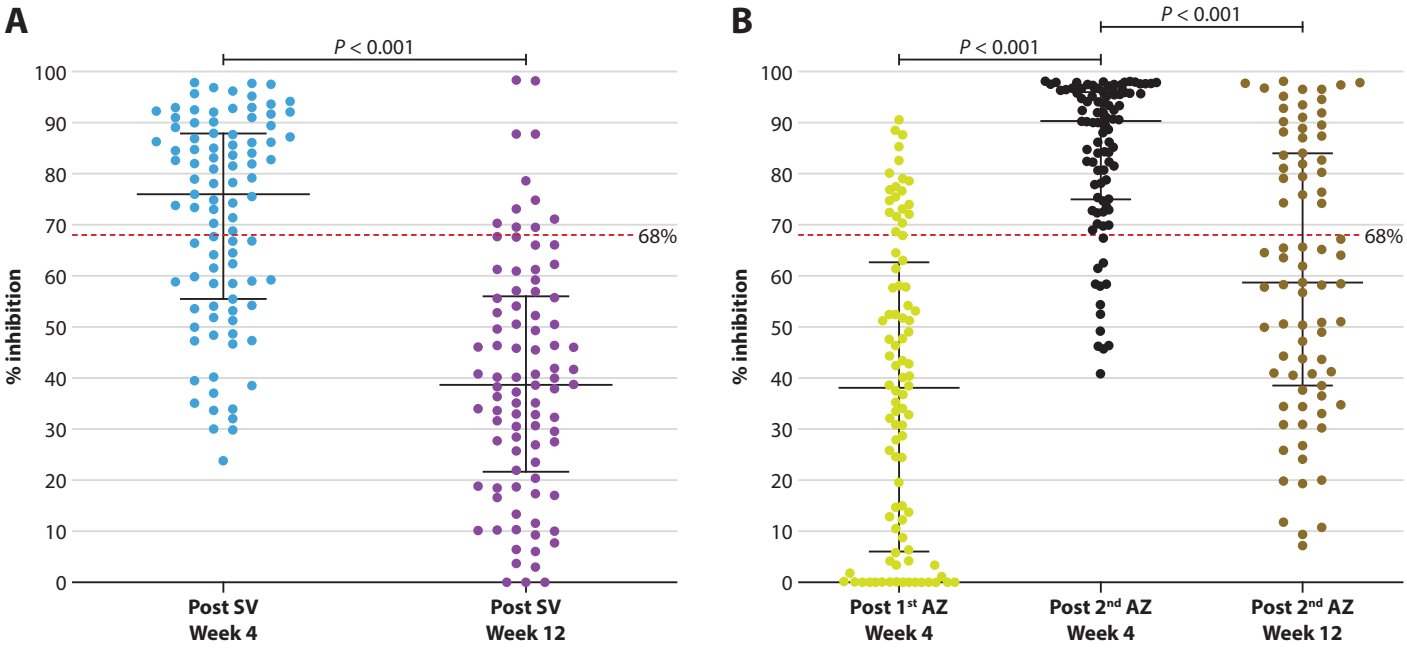

Figure 2. (A) The kinetic of the SARS-CoV-2 Neutralizing antibody using the cPass™ test (% inhibition) in health care workers who received inactivated SARS-CoV-2 vaccine (CoronaVac®, Sinovac, or SV) at 4 and 12 weeks after complete 2-dose immunization. (B) in health care workers who received ChAdOx1 nCoV-19 vaccine (Vaxzevria®, Oxford-AstraZeneca, or AZ) at 4 weeks after the first and the second dose of immunization and 12 weeks after complete 2-dose immunization.

Table 3. The seroconversion rates of health care workers who received inactivated SARS-CoV-2 vaccine (CoronaVac®, Sinovac, or SV) and ChAdOx1 nCoV-19 vaccine (Vaxzevria®, Oxford-AstraZeneca, or AZ) at 4-week after complete 2-dose vaccination and patients with COVID-19 infection who achieved the SARS-CoV2 neutralizing antibody ≥ 68% inhibition and ≥ 80% inhibition and anti-SARS-CoV-2 total antibody of ≥ 132 U/mL

Seroconversion rate	Inactivated SARS-CoV2 (SV) (N = 94)	ChAdOx1 nCoV-19 (AZ) (N = 91)	Mild COVID-19 (N = 58)	COVID-19 Pneumonia (N = 53)	*P*-value
%Inhibition ≥ 68% (N, (%))	57 (60.6)	78 (85.7)	40 (69)	49 (92.5)	< 0.001
%Inhibition ≥ 80% (N, (%))	43 (45.7)	64 (70.3)	30 (51.7)	46 (86.8)	< 0.001
SARS-CoV-2 total antibody ≥ 132 U/mL (N, (%))	67 (71.3)	91 (100)	20 (34.5)	44 (83)	< 0.001

P-value from Chi-square test

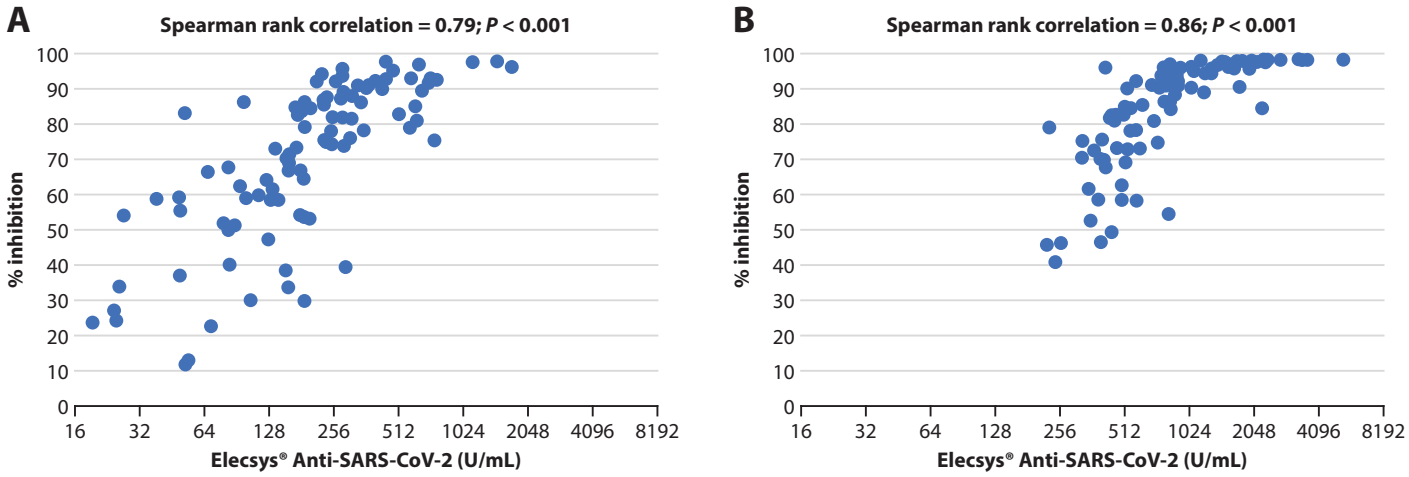

Figure 3. Correlation between the SARS-CoV-2 neutralizing antibody using the cPass™ test (% inhibition) and the anti-SARS-CoV-2 total antibody using the Elecsys™ test (U/mL) in health care workers who received inactivated SARS-CoV-2 vaccine (CoronaVac®, Sinovac, or SV) (A) and ChAdOx1 nCoV-19 vaccine (Vaxzevria®, Oxford-AstraZeneca, or AZ) (B) vaccination.

The SARS-CoV-2 Total Antibodies

At 4-week after complete vaccination or diagnosis, the median (IQR) of anti-SARS-CoV-2 total antibodies were 188.6 (115.6-312.2) U/ml in the SV group, 794.2 (497.9-1383.0) U/ml in the AZ group, 66.9 (19.7-170.2) U/ml in the mild COVID-19 group, and 794.2 (497.9-1383) U/ml in the COVID-19 pneumonia group. In the SV group, the anti-SARS-CoV-2 total antibodies among the older age group tended to be decreased but were not statistically significant (275.8 U/ml in the 20-30 years group vs 185.6 U/ml in the 51-60 years group, $P = 0.28$).

Using the US-FDA guidance of a high titer of the COVID-19 convalescent plasma, the cut-off index (COI) for the Elecsys™ test anti-SARS-CoV-2 total antibodies is ≥32 U/ml. Using the US-FDA COI criteria, 67/94 (71.3%) participants in the SV group and 91/91 (100%) participants in the AZ group had seroconversion at 4-week after complete vaccination. (**Table 3**) Notably, the anti-SARS-CoV-2 total antibodies of the AZ group were significantly higher than the COVID-19 pneumonia group ($P < 0.001$). (**Figure 1**)

According to the generalized additive models to estimate the immune marker values, in this case, the anti-SARS-CoV-2 total antibodies using the Elecsys™ kit technique (converted to BAU/ml), the vaccine efficacy of SV and AZ were 50% and 70%, respectively.[11]

Correlation Between The SARS-CoV-2 Neutralizing Antibodies and The Anti-SARS-CoV-2 Total Antibodies

The Spearman correlation coefficient between the sVNT and the anti-SARS-CoV-2 total antibodies was 0.79 for the SV group and 0.86 for the AZ group. (**Figure 3**) Interestingly, 78/91 (86.7%) participants in the AZ group had both high neutralizing antibodies (sVNT ≥ 68% inhibition) and high binding antibodies (anti-SARS-CoV-2 total antibodies ≥ 132 U/ml), compared to 55/94 (58.5%) participants in the SV group ($P < 0.001$).

Discussion

This study presented the short-term immune response of HCWs after completing the 2-dose regimens of both the SV and AZ vaccination for one and three months. In this study, the surrogate immune markers were used to predict the vaccine efficacy to protect against the SARS-CoV-2 infection and/or symptomatic disease.

The immune response of the AZ group as measured by the sVNT was higher than the SV group (85.7% vs 60.8% inhibition) at 4-week after complete immunization. Additionally, the binding antibodies, or the anti-SARS-CoV-2 total antibodies, of > 132 IU/ml was 100% in the AZ group and only 71% in the SV group. At 12-week after completing the vaccination, sVNT significantly declined to 12.2% in SV group and to 39.2% in AZ group. Similarly, the rapid decline of protective immunity was observed after the SARS-CoV-2 infection, as described by the progressive decline of the sVNT after 5-8 weeks post-infection and the decreased systemic IgA antibody level at 8 weeks post-infection.[12-13] In our study, HCWs who completed the 2-dose regimen of the SV vaccination, demonstrated a rapid decrease of sVNT at 12 weeks afterwards, and the anti-SARS-CoV-2 total antibodies were just equivalent to the mild COVID-19 patients. As the SARS-CoV-2 neutralizing antibodies level implicated the vaccine efficacy against the SARS-CoV-2 infection and symptomatic disease, the rapid reduction of the sVNT should prompt the concerns of reduced vaccine efficacy at 1-6 months after the complete SV vaccination. Moreover, the protective immunity against the SARS-CoV-2 VOC tends to require a high sVNT, though the definitive level is inconclusive. Thus, HCWS who previously received the SV vaccination should have a vaccine booster to accelerate the sVNT level. In the AZ group, though the immune response was low after the first dose, then dramatically increase after the second dose. Therefore, the interval period of the vaccination should be shortened to accelerate the sVNT level to protect against the SARS-CoV-2 VOC earlier or the heterologous prime boost regimen might be introduced to shorten duration.

The study in Chile reported the vaccine effectiveness of the SV to be 65.9% for the prevention of COVID-19.[14] In our study, the seroconversion rate was an immune marker that implicated the protective immunity against the SARS-CoV-2 infection. Therefore, the 60.8% seroconversion rate in the SV group should be equivalent to the reported vaccine effectiveness from Chile. Notably, the study in Chile was conducted during Feb-April 2021, when the circulating strains were Alpha (B.117) and Gamma (P1). Furthermore, in the SV group, the immune response tended to decrease with age, corresponding with the data from the phase 1/2 clinical trials of the SV in the healthy adults aged 60 years and older.[15] These finding supported the Thai government initial policy on vaccine allocation, which provided the SV to younger age group (18-59 years) and the AZ to the elderly (≥ 60 years). However, using multivariate analysis, no significant factors were associated with the immune response following the vaccination.

In the AZ group, a robust immune response was observed in all age groups, including the elderly, corresponding with the phase 2/3 study of the ChAdOx1 nCoV-19 vaccine in young and old adults.[16] In addition, vaccine efficacy of the AZ was similar to the study in Brazil, South Africa, and the UK.[17] Of note, the level of the AZ-induced immune response was 4-time higher than the convalescent sera after the wild-type SARS-CoV-2 infection. However, vaccine efficacy was expected to be reduced for the SARS-CoV-2 VOC. In Thailand, B1.617.2 (Delta) variant has been the main circulating SARS-CoV-2 VOC since July 2021. According to the study from the serum of the mRNA-1273 (Spikevax®, Moderna) vaccinated patients, the neutralizing antibody titers against Delta was 2.9 times less susceptible to neutralization;[18] therefore, a booster vaccine may also require after the complete AZ vaccination. A study from the United Kingdom reported that the third dose of the AZ vaccine (at 28-38 weeks after the second dose) induced high antibodies level and also boosted the T-cell responses.[19] The other vaccine strategy to improve the immune response included a heterogenous prime-boost regimen. The Com-Cov study supported the new heterogenous prime-boost COVID-19 vaccination regimen using the AZ prime and subsequently boosted with the mRNA-BNT162b2 (Comirnaty®, Pfizer–BioNTech) at 4 weeks apart had better immune response than the homologous regimen of the AZ.[20] Additionally, the study from Germany also reported that the heterogenous prime-boost with the AZ and mRNA-BNT162b2 in 12 weeks apart improved the immune responses, compared to the homologous two-dose regimens of either the AZ vaccination (with the 10-12 weeks interval) and the mRA-BNT162b2 (with the 3-week interval).[21]

A single dose of AZ also demonstrated efficacy in reducing the disease severity. Regarding the immunological mechanism of the AZ vaccine-induced protection against SARS-CoV-2, the low sVNT level after the first dose of AZ may be explained by the sole measurement of humoral response mainly from the B-cell activation. However, as a viral vector vaccine, the cellular responses (including the T cells) were also activated but were under-estimated by the sVNTs. Thus, the AZ-induced Th1 and CD8 T cell activity after the first dose of the AZ may contribute to the vaccine efficacy in ameliorating the disease severity.[3,22]

Moreover, a correlation coefficient between sVNT and anti-SARS-CoV-2 total antibodies were higher in the AZ group (0.86) than the SV group (0.79). The lower correlation coefficient may be explained by the different immunological mechanisms of the inactivated viral vaccine, including the SV, which induces a lower neutralising antibody level. Consequently, though some individuals had high titers of the SARS-CoV-2 total antibodies, the sVNT was low, indicating that the majority of anti-SARS-CoV-2 total antibodies were not neutralizing antibodies. Although other non-neutralizing antibodies might also contribute to the protective immunity,[3] the neutralization level is highly predictive of immune protection.[23] Therefore, the anti-SARS-CoV-2 total antibodies following the SV vaccination might not sufficiently represent the immune response against the SARS-CoV-2 infection, using the more accessible laboratory technique.

There were several strengths of this study. Firstly, as the HCWs were the first group who received the SARS-CoV-2 vaccinations in Thailand, our data will guide the policymakers of the Thai National Vaccine Roll-Out Program to outline the vaccine programs for the country. Secondly, the HCWs has an effective surveillance protocol to screen for the SAR-CoV-2 infection. Therefore, if no episode of SARS-CoV-2 infection was documented, the immune response should solely result from the vaccination.

This study has some limitations. Firstly, there were no definitive cut-off level of the sVNT and the SARS-CoV-2 total antibodies for protection against both wild-type SARS-CoV-2 virus and the SARS-CoV-2 VOC. Therefore, a high sVNT ≥ 68% and 80% inhibition by the US-FDA were adopted to implicate the protective immunity. Moreover, previous studies reported the high correlation between the sVNT and the $PRNT_{50}$[8] and the equivalent sVNTs of the convalescent sera of the severe COVID-19 patients. Secondly, both sVNT and the SARS-CoV-2 total antibodies only represented the humoral immune response. Further studies on the cellular immune responses after the vaccination are ongoing, comparing the T-cell activities by the ELISpot assay between the individuals who received the AZ and the SV vaccinations. Theoretically, the AZ vaccine, a viral vector vaccine platform, should have a better cell-mediated immune response than the SV vaccine, an inactivated virus vaccine platform.

In general, a highly effective vaccine with the lowest possible side effects should be offered to the front-line HCWs. From our data, the HCWs who completed 2 doses of the SV vaccination should be considered for a booster vaccine, and the HCWs who received the first dose of the AZ vaccination should shorten the interval for the second dose.

Conclusion

During the COVID-19 pandemic, the HCWs are at very high risk, as they are the front-line team to deal with the patients. Therefore, all protective measures, including non-pharmacological (including personal protective equipment) and pharmacological (including a SARS-CoV-2 vaccination), should be highly regarded. Currently, high proportions of

young HCWs in Thailand completed the SV vaccinations. However, after completing the vaccination, the short-term immune response appeared to be lower in the SV group than in the AZ group. Moreover, the HCWs in the SV group experienced a rapid decline of the immune response as early as three months after the complete vaccination. In this study, our results emphasized the urgent need for the booster vaccine for the HCWs, particularly in the SV vaccination, in amidst the circulating SARS-CoV-2 VOC such as the delta strain.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author contributions

- TP, SW, NH, LP GP, and OP contributed substantially to the conception and design of this study.
- WJ, NC, RP and PT contributed substantially to the acquisition of the data.
- WJ, NP, SW, VR, NH, TP and JS analyzed and interpreted the data.
- WJ, NP, and TP drafted the manuscript.
- LP, GS, TP, SW, NH and OP contributed substantially to the manuscript revision.
- All the authors approved the final version submitted for publication and take responsibility for the statements made in the published article.

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