RESEARCH NOTE

COMPARISON OF SARS-COV-2 ANTIBODY PRODUCTION BY 2-DOSE CORONAVAC, 2-DOSE VAXZEVRIA, 2-DOSE CORONAVAC-VAXZEVRIA HETEROLOGOUS VACCINATION AND POST-INFECTION

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Abstract. The inactivated virus vaccine CoronaVac (Sinovac) and the adenovirus vector vaccine Vaxzevria (AstraZeneca) were approved for use in Thailand to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2021 but due to early supply problems in some cases a heterologous combination of the CoronaVac for the first dose followed by the Vaxzevria for the second dose was given. We aimed to compare antibody levels among subjects who received the CoronaVac only (n = 80), Vaxzevria only (n = 80), heterologous CoronaVac-Vaxzevria (n = 54) and post-infection controls (n = 91) in order to determine if the heterologous regimen is a valid vaccination option. The geometric mean antibody levels for the CoronaVac only, Vaxzevria only, CoronaVac-Vaxzevria combined regimens and post-COVID-19 controls were 96 U/ml, 818 U/ml, 797 U/ml and 78.2 U/ml, respectively. The antibody responses to the Vaxzevria only and CoronaVac-Vaxzevria regimens were not significantly different from each other (p=0.49). The mean CoronaVac-Vaxzevria heterologous regimen antibody level was significantly (p<0.0001) greater the CoronaVac only regimen. The combination CoronaVac-Vaxzevria regimen is a potentially viable option in cases with vaccine supply problems. Further studies are needed to confirm this and to determine if the CoronaVac regimen does continue to induce low antibody responses.

Keywords: vaccine, coronavirus, Sinovac, AstraZeneca, heterologous vaccination, COVID-19

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INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a much greater demand for vaccination than supply (Sharma *et al*, 2021). Less affluent countries, including Thailand, have limited access to vaccines and must rely on vaccines available on the world market. The Thai Food and Drug Administration approved for emergency use two vaccines relatively more rapidly available for purchase: the inactivated SARS-CoV-2 vaccine, CoronaVac, from Sinovac, approved for use in individuals aged 18-59 years and reported to be moderately effective in preventing severe COVID-19 illness (Jara *et al*, 2021) and the adenovirus vector vaccine, Vaxzevria, from AstraZeneca approved for use in those aged ≥18 years, reported to elicit a robust immune response (Ramasamy *et al*, 2021).

The CoronaVac vaccine arrived in Thailand with a steady supply in February 2021 and a single batch of Vaxzevria arrived shortly thereafter. Additional Vaxzevria became available in May 2021 from a domestic vaccine production facility. Based on available scientific evidence at the time, and given the uncertainties of vaccine procurement and delivery, the Thai Advisory Committee on Immunization Practices recommended the 2-dose CoronaVac regimen be given 2-4 weeks apart and the 2-dose Vaxzevria regimen be given 10-12 weeks apart (Department of Disease Control, 2021). Early in the vaccination program there was a limited supply of vaccines and reported side-effects due to the CoronaVac (rash, anaphylaxis, and hospitalizations due to fear of the CoronaVac vaccine) resulted in some people receiving the CoronaVac vaccine for the first dose and the Vaxzevria for the second dose.

In this study we aimed to compare the antibody responses induced by 3 vaccine regimens: the CoronaVac only, the Vaxzevria only and the CoronaVac-Vaxzevria heterologous regimens and post-COVID-19 controls in order to determine the viability of the heterologous regimen for vaccination in the study population.

MATERIALS AND METHODS

Study subjects were randomly

selected from those who received one of 3 COVID-19 vaccine regimens at King Chulalongkorn Memorial Hospital during April-July, 2021: the 2-dose CoronaVac only regimen (n = 80), the 2-dose Vaxzevria only regimen (n = 80) and the 2-dose CoronaVac first dose-Vaxzevria second dose heterologous regimen and post-COVID-19 infection positive controls (n = 91). The study was conducted prospectively. In each subject serum was obtained and evaluated for SARS-CoV-2 anti-S antibodies post-vaccination by using the Elecsys anti-SARS-CoV-2 S on the Cobas e 411 analyzer according to the manufacturer's instructions (minimum detection level ≥0.8 U/ml) (Roche Diagnostics, Mannheim, Germany).

Individuals fully vaccinated with either CoronaVac or Vaxzevria, and unvaccinated COVID-19 patients who have since recovered from illness, were randomly selected representatives of the cohort as previously described (Chirathaworn *et al*, 2020).

Statistical analysis was performed using GraphPad version 9.0.2 (GraphPad Software, San Diego, CA). The Mann-Whitney U test was used to compare the differences among the groups. A p-value <0.05 was considered statistically significant.

This study was approved by the Institutional Review Board of Chulalongkorn University (approval number 192/64).

RESULTS

The mean ages of study subjects for the CoronaVac only, Vaxzevria only, CoronaVac-Vaxzevria heterologous regimens and post-COVID-19 infection controls were: 42, 48, 38 and 38 years, respectively (Table 1). The mean age in the Vaxzevria only vaccine group was higher than the other groups due to different approved age ranges for the vaccines.

All subjects who received the 2 doses of the CoronaVac regimen received them 21 days apart. The subjects who received the 2 doses of the Vaxzevria regimen received them 68-76 days apart. The subjects who received the 2 doses of the heterologous regimen received them 14-61 days apart.

The geometric mean antibody levels for those who had the CoronaVac only, Vaxzevria only, CoronaVac-Vaxzevria heterologous regimens and the post-CoVID-19 infection positive controls were: 96.4 (95% confidence interval (CI)): 76.1-122.1) U/ml, 818.1 (95% CI: 662.5-1010) U/ml, 797.2 95% (CI: 598.7-1062) U/ml and 78.2 U/ml (95% CI: 52.8-115.8), respectively (Fig 1). There was no significant difference between the heterologous regimen and the Vaxzevria regimen and between the CoronaVac regimen and the post-infection antibody level. The mean CoronaVac-Vaxzevria heterologous regimen antibody level was significantly (p<0.0001) greater the CoronaVac only regimen.

Table 1

Parameters of serological samples in this study

Characteristics	CoronaVac-CoronaVac	CoronaVac-Vaxzevria	Vaxzevria-Vaxzevria	Post-COVID-19 infection
Numbers of subjects	80	54	80	91
Female, *n* (%)	48 (60)	37 (69)	49 (61)	48 (53)
Study subject age in years				
Range	18-59	21-52	20-78	2-64
Mean	42.0	38.3	48.1	37.9
Median	43	38	49	38
Time between vaccines in days				
Range	21-21	14-61	68-76	-
Mean	21	29	70	-
Median	21	26	70	-
Time from second vaccine dose to antibody test in days				
Range	27-32	15-75	23-35	-
Mean	27.9	32.0	29.0	-
Median	28	30	29	-

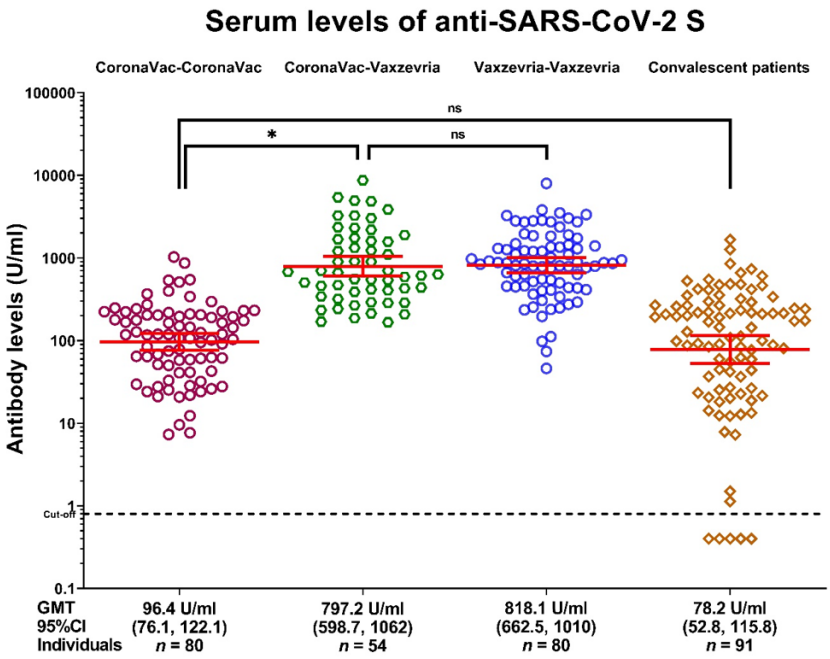

Fig 1 - Serum immunoglobulin antibodies against the SARS-CoV-2 spike (S) protein in study subjects

The long horizontal red bars denote the geometric mean titer (GMT). The short horizontal red bars denote the upper and lower 95% confidence intervals (CI). The asterisk denotes statistical significance (p<0.0001). The convalescent patients refer to the antibody levels among subjects post-COVID-19 infection.

ns: not significant; U/ml: unit per milliliter

DISCUSSION

Our study results show no significant difference in mean antibody levels between subjects who received the Vaxzevria and CoronaVac-Vaxzevria heterologous vaccines. The vaccine demand and supply inequity problem suggest a heterologous vaccine regimen needs to be explored (Lewis, 2021). Preliminary studies of safety and efficacy of the Pfizer and the Vaxzevria COVID vaccines from Spain, Germany and the United Kingdom suggest this combination is generally safe and effective (Shaw *et al*, 2021; Hillus *et al*, 2021; Schmidt *et al*, 2021; Borobia *et al*, 2021). Heterologous vaccinations may be reasonable options

in Thailand where there is vaccine supply and demand inequity. The Thai government began the CoronaVac-Vaxzevria heterologous regimen on 12 July 2021. A similar strategy is also being considered in the Philippines (Lewis, 2021) which are facing vaccine shortages and the lower antibody production resulting from the CoronaVac only regimen, as was seen in our study.

A limitation of our study was the immunoassay used for our study did not differentiate between IgM (short term) and IgG (longer term) antibodies. We did not investigate virus-specific neutralizing antibodies or T-cell response. We also did not investigate the safety and side-effect profile of the heterologous regimen. Further studies are needed to compare these regimens in multiple institutions for efficacy and safety.

In summary, our study found the CoronaVac-Vaxzevria heterologous vaccine regimen initiated antibody levels equivalent to the Vaxzevria only regimen and the CoronaVac vaccine initiated relatively low antibody levels. We conclude the CoronaVac-Vaxzevria heterologous vaccine regimen may be a viable option when insufficient Vaxzevria is available.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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