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## Safety and immunogenicity of MVC-COV1901 vaccine in older adults: Phase 2 randomized dose-comparison trial

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### ARTICLE INFO

#### Article history:

Received 5 August 2022

Revised 22 August 2022

Accepted 23 August 2022

#### Keywords:

MVC-COV1901 vaccine

Older adults

Immunogenicity

SARS-Cov-2

Immunosenescence

### ABSTRACT

**Introduction:** Older adults are subject to higher COVID-19 infection and mortality rates. Safety and immunogenicity of MVC-COV1901, a protein subunit vaccine have been demonstrated in phase 2 clinical trial for the general population, and negative correlations have been observed between immune responses and age, however, older adults were under-represented.

**Methods:** A double-blind, randomized, multi-center study compared safety and immunogenicity of high-dose (25 mcg) to mid-dose (15 mcg) of MVC-COV1901 administered 2 times 28 days apart in 420 participants of 65 years and older. The results have been stratified by the comorbidity status.

**Results:** Both high and mid-dose regimens elicited mostly mild adverse events and robust immune responses when measured as neutralizing and binding antibodies titers. High doses elicited better immune responses in the group without comorbidities.

**Conclusion:** Given the general population-associated safety and immunogenicity of MVC-COV1901, we recommend high dose for immunization of elder adults with MVC-COV1901. The clinical trial was registered at <https://clinicaltrials.gov/> (NCT04822025).

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### Introduction

Since the outbreak of the COVID-19 pandemic, the highest death rates have been consistently recorded among people older than 65 years old (World Health Organization, 2022). Although multiple countries prioritized older adults in the national vaccination strategies against SARS-CoV-2 (Our World in Data, 2022),

an increase in breakthrough COVID-19 infections was found among older adults (Haas et al., 2021). Moreover, several studies identified older age as a substantial barrier for vaccine uptake due to lack of trust, which could constrain vaccination coverage of this vulnerable population (Jantzen et al., 2022; Siu et al., 2022; Tan et al., 2022).

Whereas older population generally shows weaker immune response to vaccines due to immunosenescence (McElhaney et al., 2020; Schenkelberg, 2021; Soiza et al., 2021), the effect of age on COVID-19 vaccines immunogenicity has not been studied extensively. Pfizer BioNTech BNT162b2 clinical trials reported robust negative correlations between post-vaccination antibody responses and age (Li et al., 2021; Naaber et al., 2021). Neutralizing antibodies titers declined faster in older adults after two doses of AstraZeneca ChAdOx1 (Anderson et al., 2020). However, the results of AstraZeneca ChAdOx1 and Moderna mRNA-1273 trials were in-

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conclusive about the effect of age on SARS-CoV-2 neutralizing and binding antibodies titers (Anderson et al., 2020; Ramasamy et al., 2020). Even less is known about the effect of age on efficacy of other COVID-19 vaccines.

MVC-COV1901 is a protein subunit vaccine using the prefusion stabilized spike protein S-2P adjuvanted with CpG 1018 and aluminum hydroxide (Hsieh et al., 2021). An MVC-COV1901 dose of 15 mcg S-2P has shown favorable safety profile and robust immunogenicity in a phase 2 clinical trial and has been approved for use in Taiwan since August 2021 (Hsieh et al., 2021). The post-hoc analysis of this trial data revealed negative correlations between age and the antibody titers in 903 healthy adults from 20 to 87 years of age (Lien et al., 2021). The live-virus neutralization assay 28 days after the second dose showed a trend of decreasing immune responses to the vaccine as age increases. Older age groups also demonstrated a slower increase in binding antibodies titers from the first dose administration to 28 days after the second dose (Lien et al., 2021).

Older populations are often under-represented in most vaccine studies which generally exclude or only include a smaller proportion of older adults among the wider target population (Veronese et al., 2021). To more rigorously assess safety and immunogenicity of MVC-COV1901 vaccine in participants of 65 years and older, a double-blind, randomized study compared high-dose (25 mcg S-2P) to mid-dose (15 mcg S-2P) of MVC-COV1901. Stratification by comorbidities, such as cancer, chronic kidney disease, heart conditions, etc., was performed to better understand response to the vaccination in the more fragile subpopulations of this study.

## Methods

A prospective, randomized, dose-comparison, multi-center, double-blinded phase 2 trial was conducted at four hospitals in Taiwan. Participants were male or female of  $\geq 65$  years of age at randomization, healthy or with pre-existing medical conditions in stable condition; had not travelled overseas within 14 days prior to screening and consented to not travel overseas throughout the study period; provided written informed consent to participate in the study. Prior to the first dose of study intervention, participants must not have received any investigational intervention, licensed live-attenuated vaccines, licensed non-live-attenuated vaccines, blood product or intravenous immunoglobulin, coronavirus vaccine, immunosuppressive or immune-modifying therapy, treatment with tumor necrosis factor (TNF)- $\alpha$ , major surgery or any radiation therapy within the pre-specified time frame. Participants must not have the pre-specified medical conditions including immunosuppressive illness, history of malignancy, bleeding disorder, uncontrolled human immunodeficiency virus (HIV) infection, SARS-CoV-1 or -2 virus infections, allergy to any vaccine, fever, and any other acute or serious medical conditions which would interfere with adherence to study requirements.

The participants were randomized to receive either mid-dose (15 mcg) or high-dose (25 mcg) MVC-COV1901 in a 3:1 ratio. Randomization of participants was stratified by the presence or absence of comorbidity (comorbidity status: yes or no). Participants who had comorbidities that increased the risk of severe COVID-19 disease were defined as those who were diagnosed with at least one of the following before randomization – cancer, chronic kidney disease, chronic obstruction pulmonary disease, heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies, obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), sickle cell disease, type 2 diabetes mellitus with hemoglobin A1c (HbA1c)  $> 8\%$  at screening visit (Centers for Disease Control and Prevention, 2022). All participants were centrally assigned to randomized study intervention

using an interactive web response system with login passwords to ensure blinding for participants and investigators.

## Intervention and outcomes of interest

Each participant received two doses of mid-dose or high-dose MVC-COV1901, administered 28 days apart via intramuscular injection in the deltoid region at Day 1 and Day 29. Participants were given a diary card and instructed to record any solicited (local, systemic) and unsolicited adverse events. The severity of AEs was assessed based on the extent to which it affected participant's daily activities, as defined in the modified guidance from the US FDA (US Food and Drug Administration 2022).

The blood samples of randomized participants collected at Days 1 and 57 were measured for anti-SARS-CoV-2 neutralizing antibody titers against pseudovirus and/or live virus. The detection and characterization of neutralizing antibodies were performed by central laboratories using validated pseudovirus and/or live virus neutralization assays. The serum samples of randomized participants collected at Days 1, 29, and 57 were measured for antigen-specific immunoglobulin titers to S-2P protein. The detection and characterization of antigen-specific immunoglobulin were performed by a central laboratory using a validated enzyme-linked immunosorbent assay (ELISA) method.

## Statistical methods

Safety set included all the participants who received at least one intervention and was used in the analysis of adverse events. Sample size for this study was not based on the formal assumptions in the absence of the relevant research. Power analysis with 300 participants showed a 95% probability to observe at least one participant with an AE if the true incidence of the AE was 1% and a 78% probability if the true incidence of the AE was 0.5%. Immunogenicity was assessed for per-protocol set, which included all the participants who received two doses of intervention and had valid antibody tests. Demographic characteristics, health status, and adverse events in the mid- and high-dose groups have been summarized as means/standard deviations for continuous and frequency/percentage for categorical values. Antibodies titers were expressed as geometrical means (GMT). The comparisons between antibodies titers were based on GMT ratios. The GMT ratios with two-sided 95% confidence intervals were calculated by exponentiating the mean difference of the natural log-transformed titers (follow-up visit minus the baseline, the high-dose group minus the mid-dose group) and the corresponding confidence intervals, derived from two-samples t-test. P-values  $< 0.05$  indicated statistical significance, and p-values  $< 0.10$  indicated marginal statistical significance. The data were analyzed using SAS version 9.4 or later.

## Results

### Study design and participants

During May 20–June 24 of 2021, 444 participants of age  $\geq 65$  were screened and 420 were randomly assigned to receive a high-dose (25mcg S-2P) (n=315) or mid-dose (15 mcg S-2P) (n=105) of MVC-COV1901 vaccine. One participant was randomized to the high-dose MVC-COV1901 group, but received the mid-dose MVC-COV1901, thus the safety set comprised 314 (99.7%) participants and 106 (101.0%) participants, who received high-dose and mid-dose MVC-COV1901, respectively. Up to the data cutoff date (October 21, 2021), a total of 405 participants (305 in the high-dose group and 100 in the mid-dose group) fulfilled the criteria for inclusion in the per-protocol immunogenicity subset (Fig. 1). The

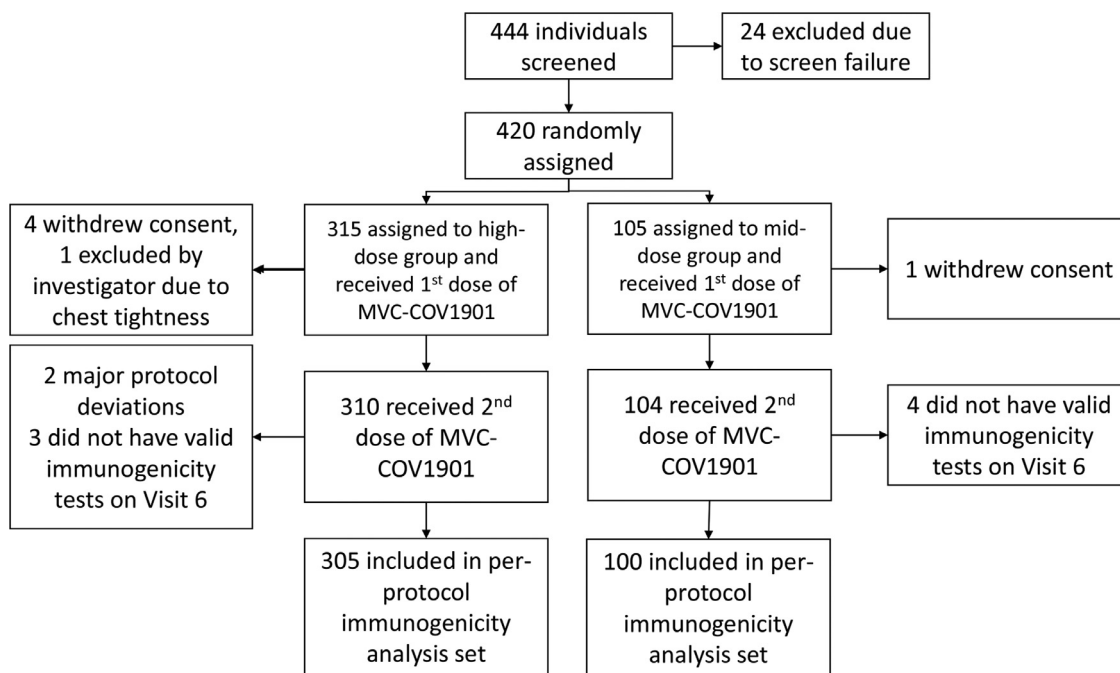


Fig. 1. Study design.

Table 1 Demographics and baseline characteristics of the participants in the safety set (N=420).

	MVC-COV1901 high-dose (25 mcg S-2P), n=314	MVC-COV1901 mid-dose(15 mcg S-2P), n=106
Mean age, years	70.5 (4.6)	70.7 (4.3)
Sex		
Females	162 (51.6)	49 (46.2)
Males	152 (48.4)	57 (53.8)
Mean body-mass index, kg/m <sup>2</sup>	25.1 (3.8)	25.0 (3.4)
HBsAg	29 (9.2)	6 (5.7)
Hepatitis C antibodies	7 (2.2)	4 (3.8)
Comorbidities		
Any	112 (35.7)	37 (34.9)
Cancer	19 (6.1)	7 (6.6)
Chronic kidney disease	36 (11.5)	7 (6.6)
Chronic obstruction pulmonary disease	11 (3.5)	6 (5.7)
Cardiovascular disease	24 (7.6)	14 (13.2)
Obesity	30 (9.6)	8 (7.5)
Type 2 diabetes mellitus with HbA1C > 8% at screening visit	17 (5.4)	2 (1.9)

Data are presented as mean (standard deviation) for continuous variables (age, body-mass index), or n (%) for categorical variables. The safety set included all participants who had received at least one dose of MVC-COV1901 vaccine.

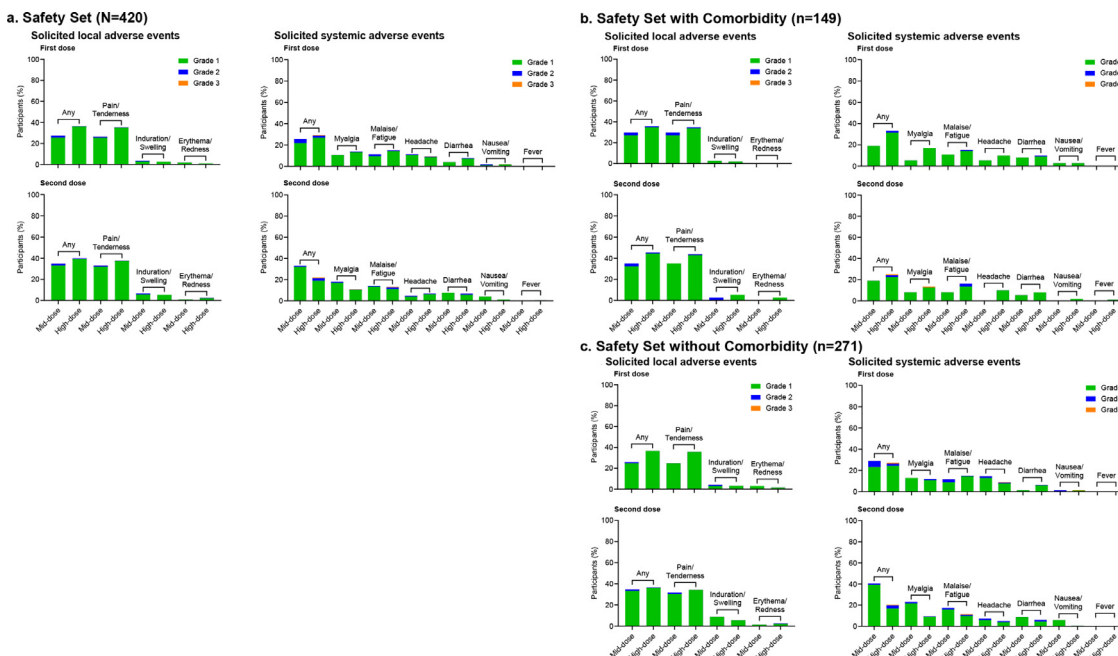
mean age of participants in the safety set was 70.6 years (standard deviation (SD) 4.5; range 65–88 years), with 209 men (49.8%) and 211 women (50.2%). All the participants were Asians. Most participants had negative serology tests for HBsAg and hepatitis C virus. A total of 149 (35.5%) participants had comorbidities, the most common of which were chronic kidney disease (43 [10.2%]), cardiovascular disease (38 [9.0%]), obesity (38 [9.0%]), followed by cancer (26 [6.2%]), type 2 diabetes (19 [4.5%]), and chronic obstruction pulmonary disease (17 [4.0%]) (Table 1).

Occurrence of mostly mild adverse events implies MVC-COV1901 safety for older adults

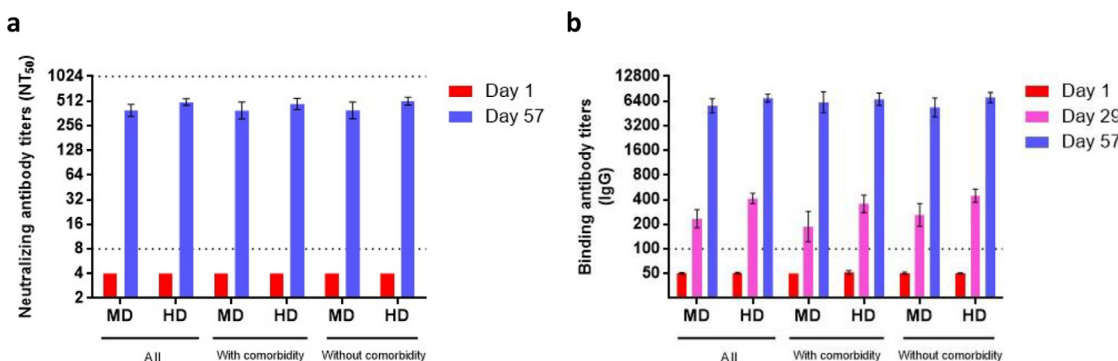
The occurrence of solicited adverse events is summarized in Fig. 2a and in supplementary Tables S1 and S2. Overall, 216 (51.4%) of 420 participants reported solicited local adverse events after receiving any dose of the study intervention. The high-dose group (168 [53.5%] of 314) outnumbered the mid-dose group (48 [45.3%] of 106) in the number of solicited local adverse events, which were mostly mild (grade 1) in severity. After any dose of MVC-

COV1901, the most common solicited local adverse event was pain/tenderness at the injection site (162 [51.6%] in the high-dose group compared with 47 [44.3%] in the mid-dose group). Solicited systemic adverse events were reported in 163 (38.8%) of 420 participants. The most common solicited systemic adverse events were myalgia (66 [21.0%] in the high-dose group compared with 27 [25.5%] in the mid-dose group) and malaise/fatigue (66 [21.0%] in the high-dose group compared with 21 [19.8%] in the mid-dose group). Fever was reported in only one participant (0.2%). The mean onset day of solicited adverse events was ≤ 3 days after the first and second dose of study intervention, with a mean duration of ≤ 3 days. A total of 121 (28.8%) of 420 participants reported 195 unsolicited adverse events (supplementary Table S3). Four (1.3%) participants in the high-dose group reported 6 unsolicited adverse events of ≥ Grade 3. No unsolicited adverse event of severity ≥ Grade 3 was related to the study intervention. No deaths or vaccine-associated enhanced disease were reported.

The proportions of solicited (supplementary Tables S4 and S5) and unsolicited (supplementary Table S6) AEs in participants with (Fig. 2b) and without (Fig. 2c) comorbidities did not differ no-



**Fig. 2.** Solicited local and systemic adverse events occurring within 7 days after first and second dose of MVC-COV1901 vaccine in mid- and high-dose groups in the safety set. (a) Safety set with all the participants (N=420). (b) Safety set with any comorbidities (n=149). (c) Safety set without any comorbidities (n=271). The comorbidities include cancer, chronic kidney disease, chronic obstruction pulmonary disease, heart conditions, obesity. Adverse events were graded as mild (grade 1), moderate (grade 2), or severe (grade 3).



**Fig. 3.** Immunogenicity of high and mid dose MVC-COV1901 vaccine in 65-88 years old. (a) Neutralizing antibody titers (NT<sub>50</sub>) against SARS-CoV-2. (b) Binding antibody titers (IgG) against SARS-CoV-2. Error bars represent 95% confidence intervals of the geometric mean titers. Black dotted lines represent lower and upper limits of detection. Comorbidities include cancer, chronic kidney disease, chronic obstruction pulmonary disease, heart conditions, obesity. HD - high dose, 25mcg S-2P of MVC-COV1901 vaccine; MD - mid-dose, 15 mcg S-2P of MVC-COV1901 vaccine.

tably and were comparable to the general safety set (Fig. 2a), supplementary Tables S1, S2 and S3). Participants with comorbidities (Fig. 2b, supplementary Table S4) reported more local AEs at high dose (40.2% after any dose) than at mid-dose (29.7% after any dose). Participants without comorbidities (Fig. 2c, supplementary Table S5) reported more systemic AEs at mid-dose (52.2% after any dose) than at high dose (35.1% after any dose).

*Immunogenicity of high- and mid-dose may be confounded by comorbidity status*

Per-protocol immunogenicity analysis is summarized in Fig. 3 and supplementary Table S7. On day 57, wild-type SARS-CoV-2 neutralizing antibody GMT in high-dose group increased to 496.4 (95% CI 452.9–544.1) with GMT ratio to the baseline of 124.1 (95% CI 113.2–136.0), whereas mid-dose group showed the respective GMT of 392.6 (95% CI 330.7–465.9) and the GMT ratio of 98.1 (95% CI 82.7–116.5) (Fig. 3a). On day 57, binding antibody GMT in

the high-dose group increased to 6964.7 (95% CI 6231.2–7784.5) with GMT ratio to the baseline of 136.68 (95% CI 122.17–152.92), whereas mid-dose showed the respective GMT of 5604.1 (95% CI 4587.1–6846.7) and the GMT ratio of 111.08 (95% CI 90.98–135.62) (Fig. 3b). Both groups with and without comorbidities showed comparable GMT and GMT ratios to the baseline on day 29 and day 57 (Fig. 3).

Table 2 summarizes GMT ratios of high- to mid- dose 28 days after the second dose. Neutralizing antibodies GMT ratio was significantly (p-value<0.05) above one (GMT ratio=1.26, 95% CI 1.05–1.52). Stratification showed higher and significant GMT ratio for the group without comorbidities (GMT ratio = 1.30, 95% CI 1.03–1.65) versus the group with comorbidities (GMT ratio = 1.20, 95% CI 0.88–1.64). Binding antibody GMT ratio showed marginally (p-value<0.10) significant increase in high-dose versus mid-dose with GMT ratio=1.24 (95% CI 0.99–1.56). The group without comorbidities showed higher GMT ratio of 1.33 (95% CI 0.99–1.77) versus the group with comorbidities (GMT ratio = 1.09, 95% CI 0.77–1.56).

**Table 2**

Geometrical mean titer ratios with 95% confidence intervals of high (25 mcg S-2P)- to mid (15 mcg S-2P)- dose groups 28 days after the second dose of MVC-COV1901 vaccine.

	Sample size of per protocol set, high-dose group/mid-dose group	Neutralizing antibodies (NT <sub>50</sub> ) geometrical mean titer ratio	P-value <sup>1</sup>	Binding antibodies (IgG) geometrical mean titer ratio	P-value <sup>1</sup>
All	305/100	1.26 (1.05, 1.52)	<b>0.014</b>	1.24 (0.99, 1.56)	<i>0.058</i>
With comorbidities <sup>2</sup>	108/33	1.20 (0.88, 1.64)	0.238	1.09 (0.77, 1.56)	0.618
Without comorbidities <sup>2</sup>	197/67	1.30 (1.03, 1.65)	0.030	1.33 (0.99, 1.77)	<i>0.056</i>

<sup>1</sup> P-value for two-samples t-test;  $p < 0.05$  bolded,  $p < 0.10$  italicized.

<sup>2</sup> Comorbidities include cancer, chronic kidney disease, chronic obstruction pulmonary disease, heart conditions, obesity.

## Discussion

This phase 2, randomized, double-blind, dose-comparison, multi-center clinical trial demonstrated safety and immunogenicity of MVC-COV1901 vaccine in older adults with and without comorbidities. A two-dose regimen of the high or mid-dose vaccine administered 28 days apart was found to be generally safe. Reactogenicity was mostly mild, and only a few cases in the high dose group reported severe AEs such as myalgia, headache or nausea. Solicited local AEs were slightly more prevalent in the high dose group, and systemic AEs were slightly more prevalent in the mid-dose group after the second dose. No substantial differences were observed in solicited and unsolicited AEs between those with and without comorbidities. MVC-COV1901 reactogenicity was slightly milder than in participants older than 65 who received two doses of NVX-CoV2373 subunit vaccine (Formica et al., 2021; Masuda et al., 2022). Notably, reactogenicity observed in our study was comparable with the NVX-CoV2373 clinical trial conducted, like our study, entirely with Asian older adults in Japan, even though the Japanese trial had a smaller sample size (Masuda et al., 2022).

Favorable immune responses were observed in both high and mid-dose groups, especially after the second dose, as indicated by the increase in neutralizing and binding antibody titers which suggests high vaccine efficacy (Khoury et al., 2021). High-dose elicited slightly higher immune responses relative to baseline than in the mid-dose group. Lack of the statistical significance between the dosages in our study may be attributed to highly heterogeneous immune response in older adults, as was demonstrated in another subunit vaccine trial (Heath et al., 2021). However, GMT ratio of high to mid-dose groups 28 days after the second dose of MVC-COV1901 vaccine was significantly higher than one and favored the high dose regimen. Previously, a phase 2 study reported that 2 different doses of NVX-CoV2373 (5- $\mu$ g or 25- $\mu$ g) delivered 21 days apart both elicited robust immune response in older adults, however, no formal statistic test have been performed to compare the regimens (Formica et al., 2021). Future trials may need to increase sample size to capture the dose-response relationships.

Further stratification of our analysis by presence of comorbidities revealed that high dose elicited slightly better immune responses in the group without comorbidities. Biological mechanism of immunosenescence provides general explanation of this finding. More morbid individuals have more weakened immune system which in turn lowers their immune response to the vaccine as evidenced by lower levels of antibodies (Schenkelberg, 2021). Due to the limited sample size, we combined all the comorbidities related to higher risks of COVID-19 (Centers for Disease Control and Prevention, 2022) into one group. The unbalanced representation of specific comorbidities in high and mid-dose groups does not allow to draw a firm conclusion about comorbidities role in the MVC-COV1901 induced immunogenicity. So far, cytosine phosphoguanine (CpG-1018) used as the vaccine adjuvant has been shown to enhance immune responses in older adults with chronic kidney disease and diabetes (Janssen et al., 2015; Hyer and Janssen, 2019),

but less is known about the other comorbidities. Targeting specific comorbidities in future trials may enhance scientific knowledge and clinical application of vaccination in more fragile populations.

Based on this analysis of safety and immunogenicity, we hypothesize that successful vaccination of older adults with high dose may enhance vaccine efficacy. Vaccine efficacy may be particularly enhanced if vaccination is protective in older individuals with comorbidities who have higher risks of COVID-19 infection, severe symptoms and hospitalization (Centers for Disease Control and Prevention, 2022). Although, the empirical determination of the antibody decay time is still ongoing, we assume that high dose will maintain the immune response for longer time. Nevertheless, individual with comorbidities and potential for adverse reactions, should carefully consider a choice of the high dose vaccines with a physician.

The stratified results by comorbidity status constitute the main strength of this study and the multi-center study design enhances the generalizability of our results. Data linking vaccine efficacy with comorbidities are often not collected because older adults with co-morbidities are usually excluded from vaccine clinical trials. In addition, older adults who are participants in phase 2 and 3 trials, generally are included because of an above-average health status (Soiza et al., 2021). Some limitations apply to our study. The results are restricted to Asian populations. This study included only older adults ( $\geq 65$  years old), thus not allowing for direct comparisons with younger populations. Exclusion of participants with prior SARS-CoV-2 infection was dictated by the extremely low SARS-CoV-2 infection rates in Taiwan at the time of the study (Taiwan Centers for Disease Control, 2022). The ongoing and future trials after the COVID-19 outbreak will be able to compare populations with and without prior SARS-CoV-2 infection. Due to limited sample size, we combined diverse comorbidities into one group to maintain the statistical power of the analysis. Future trials should include more older adults with multiple chronic conditions to determine how different levels and types of morbidity influence immune response to vaccination. Moreover, observation for longer times and adjustments for other potential confounders, such as time of vaccination, are recommended. Assessment of cellular immunity in the future studies could provide a better understanding of the immune mechanisms involved.

Compromised immune systems in older adults and especially in those with comorbidities make them more vulnerable to COVID-19 infection, which increases the burden on families and healthcare systems. We demonstrated safety and immunogenicity of MVC-COV1901 at high and mid dose regimen in older adults and suggest the high dose as preferred option unless comorbidities suggest otherwise.

## Funding source

Medigen Vaccine Biologics Corporation funded the trial and had a role in trial design.

## Ethics approval

The clinical trial was approved by four Institutional Review Boards of the participating hospitals – National Taiwan University Hospital, Taipei Medical University Shuang-Ho Hospital, Linkou Chang Gung Memorial Hospital, and Hualien Tzu Chi Hospital. All participants provided written informed consent.

## Declaration of Competing Interest

Chen C and Lien CE are employees of Medigen Vaccine Biologics Corporation. Waits A received consultancy fee from Medigen Vaccine Biologics Corporation. Other authors report no conflict of interest.

## Acknowledgments

We would like to express our deep gratitude to all the study teams and the participants at the National Taiwan University Hospital, Taipei Medical University Shuang-Ho Hospital, Linkou Chang Gung Memorial Hospital, and Hualien Tzu Chi Hospital. We would like to thank the independent data monitoring committee chair –Feng-Yee Chang, Division of Infectious Disease and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, and members –Ching-Chuan Liu, Department of Pediatrics, College of Medicine, National Cheng Kung University; Chief, Division of Pediatric Infectious Diseases, National Cheng Kung University Hospital, Hsiao-Hui Sophie Tsou, Institute of Population Health Sciences, National Health Research Institutes, Po-Yen Chen, Section of Pediatric Infectious Disease, Department of Pediatrics, Taichung Veterans General Hospital, Ming-Fang Cheng, Pediatric Infectious Diseases & Pediatric Critical Care Medicine, Kaohsiung Veterans General Hospital.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.021.

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