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Presence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibodies Among Vietnamese Healthcare Workers by Dosing Interval for ChAdOx1 nCoV-19 Vaccine

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Background. Before the SARS-CoV-2 Delta variant arrived in Vietnam, case rates suggested seroprevalence of SARS-CoV-2 was low. Beginning in March 2021, we assessed different dosing schedules and adverse events following immunization (AEFIs) for ChAdOx1 nCoV-19 vaccine among healthcare workers (HCWs).

Methods. We performed a prospective cohort study to estimate the prevalence of IgG antibodies to SARS-CoV-2 before and after ChAdOx1 nCoV-19 vaccination. We conducted antibody testing among HCWs in February 2021 (baseline), before the second dose (June–July 2021), and 1 and 3 months after the second dose. We detected antibodies to SARS-CoV-2 using Tetracore® FlexImmArray™, and surrogate neutralizing antibodies using GenScript cPass™. Neither assay can distinguish natural from vaccine-induced antibodies. We assessed AEFIs through interview post–dose 1 and 1 month post–dose 2.

Results. Before vaccination, 1/617 participants (0.16%) had antibodies to SARS-CoV-2. Of these 617, 405 were vaccinated with ChAdOx1 nCoV-19 with 4–8- (60%), 9–12- (27%), or ≥13-week (13%) intervals between the 2 doses. Three months following series completion, 99% and 97% of vaccinated participants had ≥1 sample with detectable antibodies and surrogate neutralizing antibodies against SARS-CoV-2, respectively. We observed no significant differences among those with different dosing intervals at last follow-up. All participants reported PCR testing for SARS-CoV-2 during the study; 2 (0.5%) were laboratory-confirmed. AEFIs were more frequent post–dose 1 (81%) vs post–dose 2 (21%).

Conclusions. In this population, regardless of dosing interval, ChAdOx1 nCoV-19 induced antibodies within 3 months of the second dose. These findings may offer flexibility to policymakers when balancing programmatic considerations with vaccine effectiveness.

Keywords. SARS-CoV-2; seroprevalence; vaccination.

Vietnam responded to the coronavirus disease 2019 (COVID-19) pandemic with strong and sustained containment measures, including border closures, strict quarantine of exposed individuals, and isolation of suspected and confirmed cases [1]. This early response contributed to the low seroprevalence of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the population before the arrival of the B.1.617 (Delta) variant in April 2021. Most commercially available assays detect antibodies against the nucleocapsid (anti-N) protein, the spike (anti-S) protein, or both. Both natural infection and Vero cell vaccines trigger antibody responses to the nucleocapsid protein. Natural infection,

Vero cell vaccines, and vaccines specifically targeting the spike protein can trigger antibody responses to the spike protein. In a study conducted in Vietnam in late 2020, only 7 (0.24%) of 2954 residents of communities with previously documented cases of COVID-19, and none of 149 resident healthcare workers (HCWs) providing care to patients with COVID-19, had detectable anti-N immunoglobulin G (IgG) antibodies to SARS-CoV-2 [2]. The low number of infections identified in the context of high volumes of polymerase chain reaction (PCR) testing and targeted serologic testing is consistent with the hypothesis that seroprevalence was likely low throughout Vietnam. Beginning 29 April 2021, the Delta variant arrived in the country, and case counts began to climb, although outbreaks were mostly concentrated in southern provinces [3].

In April 2021, Vietnam moved into the vaccination phase of pandemic control. By January 2022, the government had acquired approximately 175 million doses of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine, and over 153 million doses

had been administered in its population of 98.5 million [3]. By March 2022, approximately 81% of Vietnam's total population over 12 years of age had received at least 1 dose of COVID-19 vaccine [4].

In the wake of the Delta variant, an influx of vaccines enabled healthcare and quarantine facilities to initiate rapid vaccination of high-risk workers using 2 doses of ChAdOx1 nCoV-19 vaccine, administered 1 month apart. A subset of these facilities participated in a baseline seroprevalence study beginning in late 2020, which provided an opportunity to evaluate changes in the prevalence of antibodies to SARS-CoV-2 following vaccination. One participating center, the National Hospital for Tropical Diseases (NHTD), is a 1000-bed tertiary referral hospital in Hanoi and is designated by the Ministry of Health as an official COVID-19 treatment center for Vietnam's northern provinces.

Guidelines set by Vietnam's National Expanded Program on Immunization state that all vaccines imported into the country must be evaluated and approved [5, 6]. Randomized controlled trials of vaccine efficacy are not required if the vaccine has been prequalified or has received emergency use listing by the World Health Organization, as is the case for the ChAdOx1 nCoV-19 vaccine [5, 6]. To contribute to the evidence base for future policymaking in Vietnam, we adopted 2 primary objectives for this study: estimate the prevalence of IgG antibodies to SARS-CoV-2 among members of a cohort of HCWs before and after receipt of the ChAdOx1 nCoV-19 vaccine and compare the prevalence of IgG antibodies with SARS-CoV-2 among persons receiving different dosing intervals of the 2-dose regimen. As a secondary objective, we also described adverse events following immunization (AEFIs) in the same population.

METHODS

Study Design

We performed a prospective cohort study of HCWs at NHTD. All consenting hospital workers participated in a baseline COVID-19 seroprevalence survey in February 2021. A subset of workers with regular exposure to patients with SARS-CoV-2 infection received their first dose of the ChAdOx1 nCoV-19 vaccine beginning March 2021 and were invited to participate in a cohort study to evaluate the immune response to ChAdOx-1 after different dosing schedules. At that time, Vietnam was experiencing the most severe wave of COVID-19 to that point, making it difficult to standardize dosing intervals as NHTD rushed to vaccinate HCWs. Participants had blood collected at 3 additional points in time: on the day of the second dose (between June and July 2021; post–dose 1), 31–35 days after receipt of the second dose (1 month post–dose 2), and 77–91 days after receipt of the second dose (3 months post–dose 2). Participants were interviewed regarding their

exposures and health conditions at 3 points in time: prior to vaccination, post–dose 1, and 1 month post–dose 2 (Figure 1). Participants were interviewed regarding AEFIs at 2 points in time: post–dose 1 and 1 month post–dose 2. We solicited report of any unusual signs following vaccination (yes/no/unknown) as well as responses (yes/no/unknown) to experience of specific symptoms including dates. All interviews were administered by trained interviewers using digital tablets for real-time data entry.

Data Collection

All participants were interviewed using a structured questionnaire to ascertain basic demographic information, clinical duties, exposure to known cases of COVID-19, travel history, testing history, symptoms of COVID-19 over the previous 12 months (baseline) or since the last survey (post–dose 1 and 1 month post–dose 2), and underlying health conditions. Adverse events following immunization were confined to experiences of symptoms within a 7-day window following receipt of the first or second vaccine dose, respectively. We verified vaccine dosing intervals using hospital vaccine administration data.

Laboratory Procedures

Approximately 6 mL of venous blood was collected using a Becton Dickinson Vacutainer serum tube and was transported to a Ministry of Health laboratory within 6 hours of collection. Serum was separated by centrifugation and was stored at −20°C prior to testing. All assays were performed according to the manufacturers' instructions.

Baseline specimens were tested using the Euless Anti-SARS-CoV-2 assay to assess total IgG enzyme-linked immunosorbent assay (ELISA) against nucleocapsid proteins (Roche Diagnostics, Switzerland), indicating the presence of natural infection.

At subsequent time points, we tested specimens using the Tetracore FlexImmArray SARS-CoV-2 Human IgG Antibody Test (Tetracore, Inc, Rockville, MD). This assay contains 5 specific SARS-CoV-2 target proteins: the nucleocapsid protein (N), the receptor-binding domain (RBD), the spike protein trimer (S), the S1 subunit of spike protein (S1), and the N-terminal domain of the S1 protein (NS). This assay measures relative fluorescent intensity (RFI), the ratio of the median fluorescent intensity (MFI) of the test sample to the average MFI of duplicate low-positive samples provided with the kit. We considered specimens to be positive for SARS-CoV-2 antibodies according to the manufacturer's instructions: if the microsphere RFI was 1.0 or greater for any 3 of the 5 antigens the specimen was considered to have IgG antibodies against SARS-CoV-2. The Tetracore assay is not validated to distinguish immunity induced by natural infection from immunity induced by vaccination with
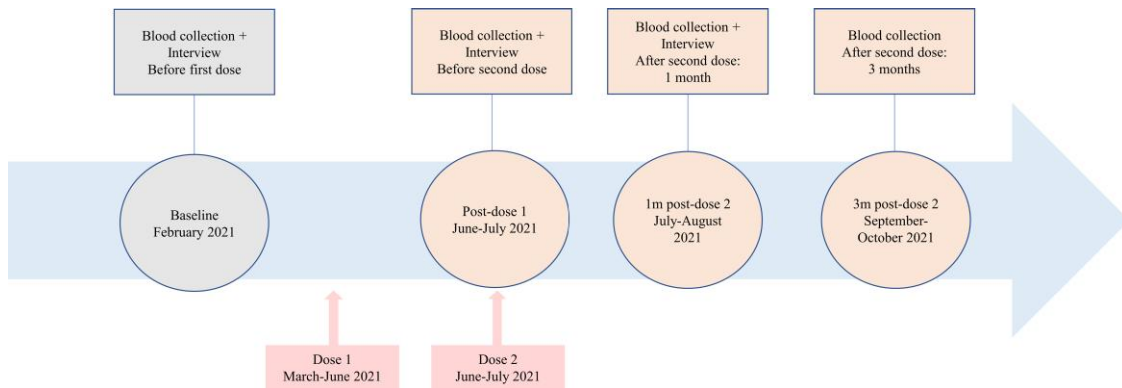
Figure 1. Study timeline for assessing SARS-CoV-2 seroprevalence and adverse events following immunization among a prospective cohort of Vietnamese healthcare workers before and after receiving ChAdOx1 nCoV-19 vaccine. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 1m, 1 month; 3m, 3 months.

ChAdOx1 nCoV-19; thus, we were unable to address this question in our study population.

Additionally, we tested postvaccination specimens using the GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript, Piscataway, NJ). According to the manufacturer's package insert, this assay has shown 100% (95% confidence interval [CI]: 87.1–100.0%) positive agreement and 100.0% (95% CI: 95.8–100.0%) negative agreement with plaque reduction neutralization (PRNT) 50 and PRNT90, respectively, in clinical studies. Specimens with 30% or greater signal inhibition were considered to have neutralizing antibodies against RBD of SARS-CoV-2, while those with less than 30% signal inhibition were not.

Statistical Analysis

The primary outcome was the presence of SARS-CoV-2 antibodies, defined by a positive Tetracore sample (described above). As a secondary outcome, we also examined the presence of neutralizing (ie, functional) antibodies, defined by GenScript positivity (described above). Results are presented as case counts and percentages (% participants positive according to Tetracore or GenScript tests, respectively).

We used stratified analysis to describe the outcome distribution by a range of independent variables, including demographic measures (age, sex, education, type of job), pre-existing health conditions, and level of exposure to potential SARS-CoV-2 infection. Using a structured questionnaire, we quantified levels of exposure based on the self-reported frequency of close contact between COVID-19 cases and HCWs inside and outside their healthcare facilities, as well as travel history visiting other high-risk areas. Kaplan-Meier curves were generated to illustrate seropositivity over time. We used a log-rank test to determine significant differences when stratifying by dosing interval. Next, we ran univariable analyses separately for the outcomes of Tetracore and GenScript

seropositivity. Variables with a level of significance of 0.15 or less were included in a Cox proportional hazards model to estimate effect size (reported as hazard ratios and 95% CI) between seropositivity over time and exposures potentially associated with seropositivity. Participants were excluded from the analysis if they only had data prior to vaccination or at 3 months post–dose 2. The number and types of AEFIs are reported by dose. All calculations were performed using STATA version 14.2 (StataCorp, College Station, TX, USA). This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (see eg, 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

RESULTS

Description of Cohort

The analysis sample included 405 vaccinated participants observed from February to October 2021, with 201 (50%) ultimately completing follow-up at 3 months post–dose 2 (Figure 2). Participants were primarily female (59%) and younger than 40 years of age (80%). Sixty-seven (17%) reported a current or past history of chronic illness. All participants received 2 doses of ChAdOx1 nCoV-19 vaccine, with 4–8-week (60%), 9–12-week (27%), or 13-week or more (13%) dosing intervals. People receiving their second vaccine dose at a 4–8-week interval were more likely be female, highly educated, and nurses (Table 1).

Participants reported experiencing multiple COVID-19–like symptoms during the study, including sore throat (40%), cough (39%), and runny nose (36%). Few participants (12%) experienced fever combined with respiratory symptoms. Symptoms were primarily reported at baseline, with fewer reports during the vaccination period. All participants (100%) reported PCR testing for COVID-19, and nearly 60% reported antibody
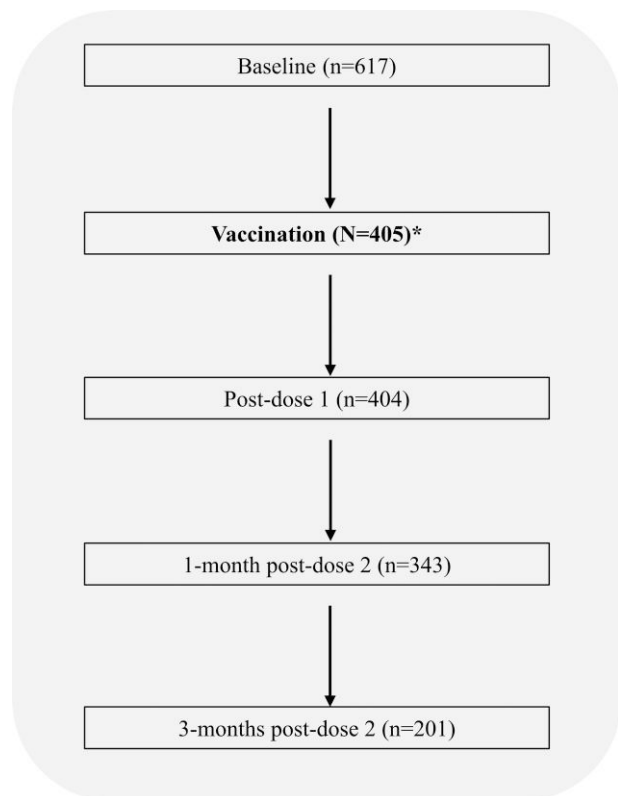
Figure 2. Participant flow of a cohort of Vietnamese healthcare workers from baseline through 3 study rounds before and after vaccination with ChAdOx1 nCoV-19 (February–October 2021). Only vaccinated participants are included in the final analysis. *Final sample for analysis.

testing unrelated to the study, although only 2 (0.5%) reported having laboratory-confirmed COVID-19. Only 14 (4%) of participants reported contact with confirmed COVID-19 cases or people exhibiting COVID-19–like symptoms outside their place of work (Table 2).

Seroprevalence
At baseline, 1 (0.16%) of 617 participants had antibodies against SARS-CoV-2 by prior infection. At post–dose 1 (time of the second dose), seroprevalence began increasing (Figure 3). By 10 weeks after the first dose, 55% of participants had antibodies against SARS-CoV-2 and 48% had neutralizing antibodies. By the end of the study, 99% and 97% of participants had at least 1 sample with detectable antibodies and neutralizing antibodies, respectively. Stratification by different dosing intervals shows that participants who received their second dose at shorter intervals (4–8 weeks) reached seropositivity more quickly compared with participants with longer intervals (9–12 weeks or ≥13 weeks) between doses (P < .001) (Figure 4A). At the time of their second dose, participants with 4–8-week dosing intervals had a higher prevalence of antibodies and neutralizing antibodies compared with

participants with 9–12-week or 13-week or more intervals (P < .001) (Figure 4B and 4D). However, this difference was reduced following the second-dose vaccination for longer interval dosing groups. By the end of the 3-month follow-up period, the dosing interval no longer correlated with differences in seroprevalence or the presence of neutralizing antibodies.

After the first dose, univariable analyses of incidence density over the course of the study demonstrated that women were more likely than men to have the presence of antibodies (11.1 per 100 person-weeks [9.8–12.6] and 9.4 per 100 person-weeks [8.1–11.0], respectively) and neutralizing antibodies (9.8 per 100 person-weeks [8.6–11.2] and 8.3 per 100 person-weeks [7.1–9.7], respectively) (Supplementary Table 1). However, inclusion of sex in the multivariable model did not alter the degree or level of association between dosing interval and outcomes (Supplementary Table 2).

Adverse Events Following Immunization
At post–dose 1, 81% of participants reported experiencing AEFIs, and 39% reported 3 or more symptoms. At post–dose 2, 21% reported AEFIs (Supplementary 3). Pain and swelling at the injection site was the most reported symptom (60% post–dose 1; 16% post–dose 2), followed by fever (48% post–dose 1; 2% post–dose 2) and muscle pain (33% post–dose 1; 3% post–dose 2). All symptoms were reported more frequently at post–dose 1 (Figure 5).

DISCUSSION

In this population of HCWs, the ChAdOx1 nCoV-19 vaccine was effective in provoking an antibody response within the first 3 months of receiving the 2-dose series, regardless of the interval between the administration of the first and second doses. We found that dosing intervals from 4 to 18 weeks resulted in similar seroprevalence through a 77–91-day follow-up period. These doses of the ChAdOx1 nCoV-19 vaccine were among the first administered in the country and were introduced concurrently with the arrival of the Delta variant of SARS-CoV-2. This, combined with the increased risk of exposure at a major national COVID-19 hospital, infused urgency into the vaccination program and the need to gather some evidence of the effects of the vaccine. This "real world" scenario has played out in hospitals globally during the pandemic; it allowed us to assess dosing intervals that may not have been practical to study in the context of a randomized controlled trial. Additionally, as regulatory guidelines mandate that all new vaccines must be evaluated prior to use, these results contribute to evidence supporting the implementation of the ChAdOx1 nCoV-19 in Vietnam.

Although shorter dosing intervals in our study resulted in antibody detection more quickly, other studies suggest that earlier vaccine-induced immunity may wane more quickly [7, 8].

Table 1. Characteristics for Study Cohort of Vietnamese Healthcare Workers Vaccinated With ChAdOx1 nCoV-19

Demographic Characteristics	Total No. (%)	Vaccine Dosing Interval,[a] n (%)			
		4–8 Weeks (n = 241; 59.5%)	9–12 Weeks (n = 111; 27.4%)	≥13 Weeks (n = 53; 13.1%)	P
Sex					.003
Female	239 (59.0)	159 (66.0)	54 (48.6)	26 (49.1)	
Age, median (IQR), years	33.1 (28.5–39.1)	34.4 (28.1–39.6)	32.0 (28.7–36.5)	318. (28.8–38.4)	.190
≤30 years	157 (38.8)	87 (36.1)	47 (42.3)	23 (43.4)	.173
31–40 years	167 (41.2)	98 (40.7)	51 (45.9)	18 (34.0)	
41–50 years	57 (14.1)	38 (15.8)	9 (8.1)	10 (18.9)	
>50 years	24 (5.9)	18 (7.5)	4 (3.6)	2 (3.8)	
Educational level					.004
Less than high school	16 (4.0)	14 (5.8)	1 (0.9)	1 (1.9)	
High school	15 (3.7)	12 (5.0)	3 (2.7)	0 (0)	
Some college	108 (26.7)	59 (24.5)	41 (36.9)	8 (15.1)	
Undergraduate or graduate degree	266 (65.7)	156 (64.7)	66 (59.5)	44 (83.0)	
Marital status					.543
Not married	87 (21.5)	52 (21.6)	25 (22.5)	10 (18.9)	
Married and living together	311 (76.8)	183 (75.9)	86 (77.5)	42 (79.2)	
Divorced/separated/widowed	7 (1.7)	6 (2.5)	0 (0)	1 (1.9)	
Occupation					.020
Doctor/medical doctor	113 (27.9)	59 (24.5)	34 (30.6)	20 (37.7)	
Nurse/midwife	152 (37.5)	94 (39.0)	40 (36.0)	18 (34.0)	
Technician	45 (11.1)	19 (7.9)	19 (17.1)	7 (13.2)	
Housekeeper	5 (1.2)	2 (0.8)	2 (1.8)	1 (1.9)	
Patient transport staff	4 (1.0)	2 (0.8)	2 (1.8)	0 (0)	
Sanitation worker	12 (3.0)	12 (5.0)	0 (0)	0 (0)	
Car security and parking	12 (3.0)	11 (4.6)	1 (0.9)	0 (0)	
Other	62 (15.3)	42 (17.4)	13 (11.7)	7 (13.2)	
At least 1 comorbidity[b]	67 (16.5)	33 (13.7)	21 (18.9)	13 (24.5)	.115

N = 405.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Overall range: 4.3–18.4 weeks.

[b]Includes dengue fever, cancer, diabetes, hypertension, HIV/other immunodeficiency syndrome, heart disease, asthma, chronic lung disease, chronic liver disease, chronic blood disease, chronic kidney disease, chronic neurasthenia, organ or bone marrow recipient, and other chronic diseases.

Furthermore, longer dosing intervals may correlate with higher quantitative antibody levels [7, 8] and the development of neutralizing antibodies, which are critical for immune protection [9]. In comparing immunity levels among another group of Vietnamese HCWs, previously uninfected participants (n = 144) were sampled before and after ChAdOx1 nCoV-19 vaccination and assessed for neutralizing antibodies using GenScript [10]. All participants had a 6-week dosing interval. At 3 months post–dose 1 (6 weeks post–dose 2), antibody prevalence had decreased from a peak of 98.1% (measured at 2 weeks post–dose 2) to 94.7%. This could signal a waning effect, as seen with other COVID-19 vaccines, particularly against new variants [11, 12]. Longer follow-up periods are warranted to further understand effects.

We also found large differences in AEFIs following the first dose compared with the second dose. Over 80% of HCWs reported symptoms after the first dose. Symptoms were much more common after the first dose than after the second dose, with injection site pain and swelling, fever, and muscle aches most frequently reported. Post–dose 2 AEFIs were reported by fewer than 20% of participants in our cohort. These data corroborate existing evidence from other studies [13–15] and may be important for workforce management during the implementation of future workplace ChAdOx1 nCoV-19 vaccination efforts.

Although identifying the reactivity of the nucleocapsid protein is currently the best tool available [16], the inability to distinguish between antibody response conferred by vaccination or SARS-CoV-2 infection is a limitation as it introduces uncertainty that antibody response was provoked by ChAdOx1 nCoV-19 vaccination. However, the study took place in northern Vietnam, where COVID-19 cases were less prevalent compared with other parts of Vietnam during the study period, and a history of low seroprevalence has been found [4]. Further, the fact that very few participants reported symptoms of COVID-19 during the vaccination period, virtually 100% were tested for SARS-CoV-2 by PCR, fewer than 1% reported PCR positivity, and all participants experienced seroconversion supports the notion that most immunity was vaccine-induced. Other important questions extend beyond the scope of this

Table 2. Self-Report of Clinical and Exposure History Among a Cohort of Vietnamese Healthcare Workers Receiving ChAdOx1 nCoV-19 Vaccine

	Total, n (%)	Baseline[a] (n = 340)	Post–Dose 1 (n = 405)	Post–Dose 2 (n = 340)
Symptoms experienced since last interview[b]				
Sore throat	162 (40.0)	154 (45.3)	15 (3.7)	2 (0.6)
Cough	157 (38.8)	148 (43.5)	18 (4.4)	1 (0.3)
Runny nose	144 (35.6)	138 (40.6)	18 (4.4)	2 (0.6)
Fatigue	122 (30.1)	103 (30.3)	22 (5.4)	12 (3.5)
Headache	118 (29.1)	97 (28.5)	29 (7.2)	5 (1.5)
Fever 38°C	70 (17.3)	45 (13.2)	27 (6.7)	4 (1.2)
Muscle pain	63 (15.6)	34 (10.0)	27 (6.7)	12 (3.5)
Abdominal pain	43 (10.6)	36 (10.6)	6 (1.5)	2 (0.6)
Chills	37 (9.1)	25 (7.4)	10 (2.5)	3 (0.9)
Diarrhea	30 (7.4)	25 (7.4)	6 (1.5)	1 (0.3)
Nausea/vomiting	20 (4.9)	15 (4.4)	5 (1.2)	2 (0.6)
Chest pain	14 (3.5)	12 (3.5)	2 (0.5)	0 (0)
Shortness of breath	13 (3.2)	12 (3.5)	1 (0.2)	0 (0)
Loss of smell/taste	10 (2.5)	10 (2.9)	0 (0)	0 (0)
Other symptoms	3 (0.7)	0 (0)	1 (0.2)	2 (0.6)
Fever + at least 1 respiratory symptom	50 (12.3)	10 (2.5)	1 (0.3)	10 (2.5)
Fever + at least 1 respiratory symptom + at least 1 other symptom	40 (9.9)	9 (2.2)	1 (0.3)	9 (2.2)
Had a PCR test	405 (100)	315 (92.6)	405 (100)	338 (99.4)
Had a COVID-19 antibody test	240 (59.3)	56 (16.5)	161 (39.8)	66 (19.4)
Reported infection with COVID-19	2 (0.5)	1 (0.3)	0 (0)	1 (0.3)
Visited a medical facility other than place of work	146 (36.0)	129 (37.9)	24 (5.9)	10 (2.9)
Reported moving residence between provinces	285 (70.3)	276 (81.2)	123 (30.4)	14 (4.1)
Interacted with patients and family members of patients with confirmed COVID-19 or COVID-19–like symptoms	121 (35.6)	158 (39.0)	115 (33.9)	43 (81.1)
Had contact with anyone with confirmed COVID-19 or COVID-19–like symptoms at work	223 (55.1)	121 (35.6)	158 (39.0)	115 (33.9)
Had contact with anyone with confirmed COVID-19 or COVID-19–like symptoms outside of work	14 (3.5)	3 (0.9)	9 (2.2)	2 (0.6)

N = 405.

Abbreviations: AEFI, adverse event following immunization; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

[a]Baseline participants include only those who were vaccinated with ChAdOx1 nCoV-19 (340/617). For this time point, all responses are solicited from January 2020 to time of interview.

[b]These symptoms were reported by participants at any time point since the last interview, compared with AEFIs that were solicited separately and confined to reports within a 7-day window since the first or second vaccine dose, respectively.
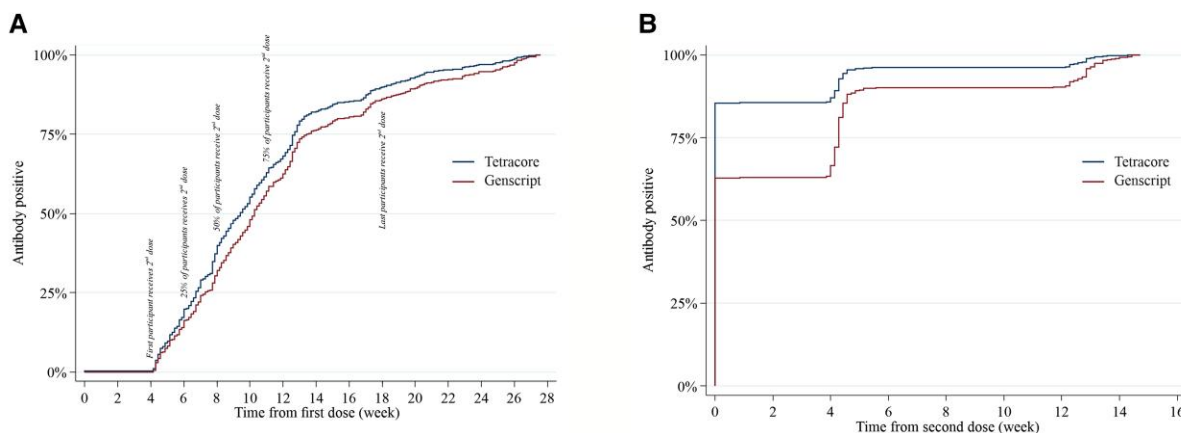

Figure 3. Proportion of participants with presence of antibodies (Tetracore) and neutralizing antibodies (GenScript) against SARS-CoV-2 by time since first (A) or second (B) dose. The first participant had their second dose 4.3 weeks after their first dose, while the last participant had their second dose 18.4 weeks after their first dose. The time when quartiles of participants received second doses of ChAdOx1 nCoV-19 is indicated on the figure.

study. First, a 3-month period is not sufficient to evaluate the duration of protection, a critical factor in determining the need for 1 or more booster doses. Second, our use of qualitative antibody testing precludes the description of variation in antibody concentrations over time in individual participants. Rather, our study looks at group-level dynamics with respect
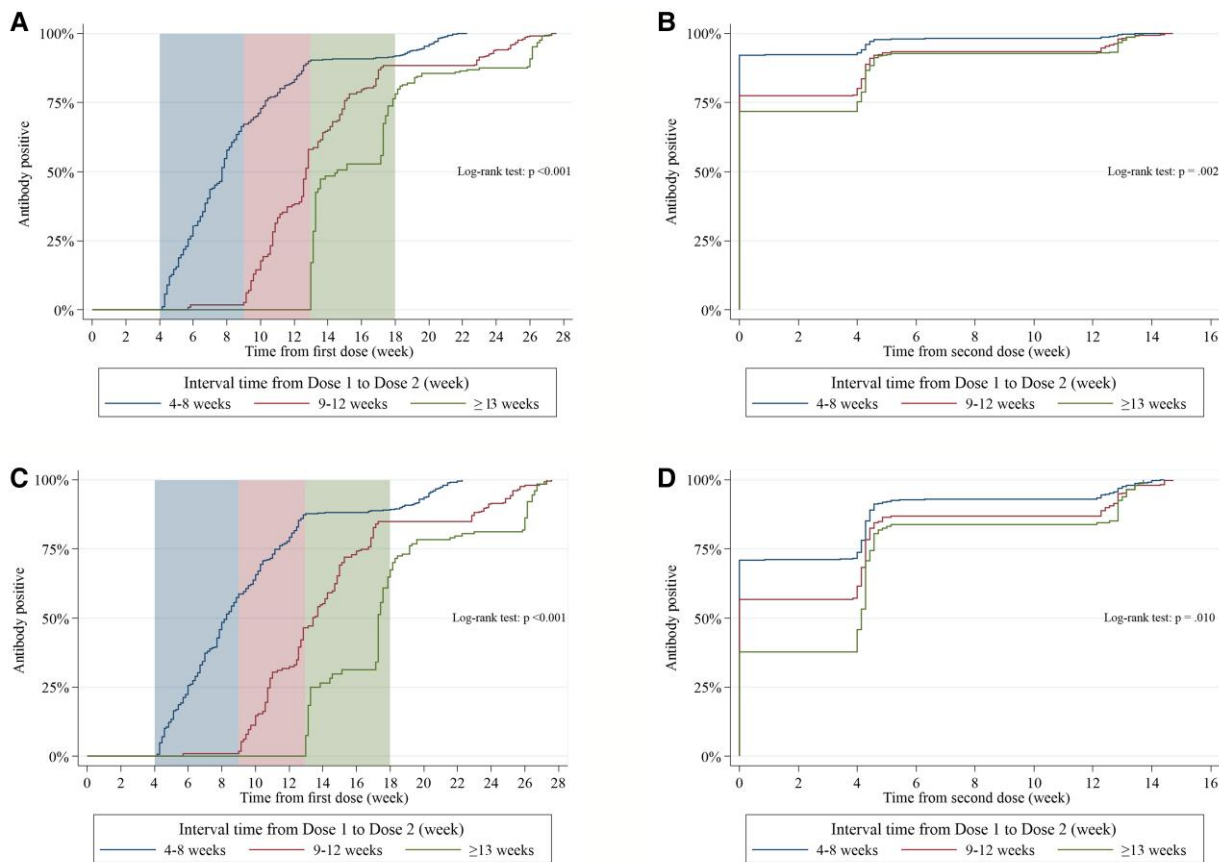
Figure 4. Proportion of participants with presence of antibodies (Tetracore) (*A*, *B*) and neutralizing antibodies (GenScript) (*C*, *D*) against SARS-CoV-2 by time since first (left) or second (right) dose, 3 dosing intervals. Shading indicates the time frame during which participants received their second dose of ChAdOx1 nCoV-19, corresponding to a dosing interval of 4–8 weeks (blue), 9–12 weeks (red), or ≥13 weeks (green). Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
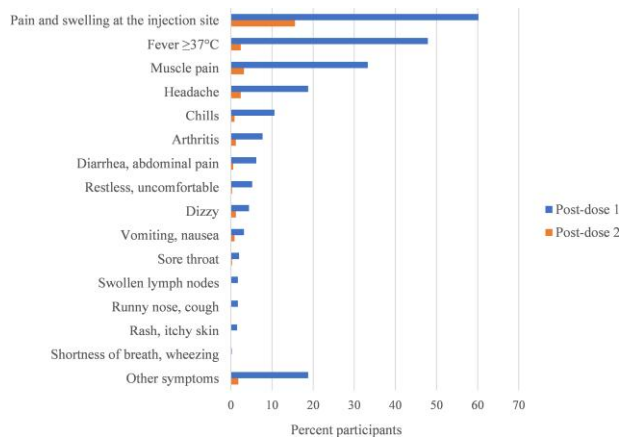
Figure 5. Type and prevalence of adverse events following immunization reported by participants within 7 days following the first and second dose of ChAdOx1 nCoV-19.

to dosing intervals, which is still relevant for national immunization policy. Third, humoral antibody is also only 1 component of the adaptive immune system. We were not able to collect information on cellular components of immunity, such as T cells or nonspecific immune cells. Fourth, because we had samples only from set time points, we are uncertain when individual participants first had detectable or functional antibody. Future studies may consider addressing some of these questions.

CONCLUSIONS

In this population of HCWs, ChAdOx1 nCoV-19 vaccination was followed by antibody response within the first 3 months of receiving the 2-dose series, regardless of the dosing interval. Future ChAdOx1 nCoV-19 vaccination campaigns for HCWs in Vietnam may prioritize high coverage, knowing that modest variability in dosing intervals is unlikely to substantially and negatively affect seroprevalence. Future studies should aim to assess the duration of protection and subsequent need for booster doses.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

References

1. Duong DA-O, Le VT, Ha BTT. Controlling the COVID-19 pandemic in Vietnam: lessons from a limited resource country. Asia Pac J Public Health **2020**; 32:161–2.
2. Hasan T, Pham TN, Nguyen TA, et al. Sero-prevalence of SARS-CoV-2 antibodies in high-risk populations in Vietnam. Int J Environ Res Public Health **2021**; 6353:18.
3. General Statistics Office of Vietnam. Infographic population, labour and employment in 2021. Available at: https://www.gso.gov.vn/en/data-and-statistics/2022/01/infographic-population-labour-and-employment-in-2021/. Accessed 2 April 2022.
4. World Health Organization. Coronavirus disease (COVID-2019) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed 17 March 2022.
5. Ministry of Health of the Socialist Republic of Vietnam. Circular no. 07/2018/TT-BYT: Detailing some articles on pharmaceutical business of the Law on Pharmacy and the Decree No. 54/2017/ND-CP dated May 08, 2017 of the Government detailing a number of articles and measures for implementation of the Law on Pharmacy. Signed in Hanoi on April 12, 2018. Available at: https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Thong-tu-07-2018-TT-BYT-huong-dan-kinh-doanh-duoc-cua-Luat-duoc-Nghi-dinh-54-2017-ND-CP-381621.aspx. Accessed 18 April 2022.
6. Ministry of Health of the Socialist Republic of Vietnam. Circular no. 11/2021/TT-BYT: Providing guidelines for registration for marketing authorization of COVID-19 vaccines for emergency use. Signed in Hanoi on August 19, 2021. Available at: https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Thong-tu-11-2021-TT-BYT-huong-dan-dang-ky-luu-hanh-vac-xin-Covid19-truong-hop-cap-bach-485321.aspx. Accessed 18 April 2022.
7. Flaxman A, Marchevsky NG, Jenkin D, et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet **2021**; 398:981–90.
8. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet **2021**; 397:881–91.
9. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med **2021**; 27:1205–11.
10. Chau NVV, Nguyet LA, Nguyet LA, et al. Immunogenicity of Oxford-AstraZeneca COVID-19 vaccine in Vietnamese health-care workers. Am J Trop Med Hyg **2022**; 106:556–61.
11. Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet **2022**; 399:924–44.
12. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance—VISION network, 10 states, August 2021–January 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:255–63.
13. Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med **2021**; 385:2348–60.
14. Hillus D, Schwarz T, Tober-Lau P, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. Lancet Respir Med **2021**; 9:1255–65.
15. Wanlapakorn N, Suntronwong N, Phowatthanasathian H, et al. Safety and immunogenicity of heterologous and homologous inactivated and adenoviral-vectored COVID-19 vaccine regimens in healthy adults: a prospective cohort study. Hum Vaccin Immunother **2022**; 24:1–10.
16. Demmer RT, Baumgartner B, Wiggen TD, et al. Identification of natural SARS-CoV-2 infection in seroprevalence studies among vaccinated populations. Mayo Clinic Proc **2022**; 97:754–60.