original article

Outcome after single dose of ChAdOx1 vaccine against SARS-CoV-2 infection at 16 weeks post-vaccination among healthy adults in Saudi Arabia

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BACKGROUND: The rate of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection and immunogenicity of a single dose of ChAdOx1 vaccine at 16 weeks post-vaccination among young and healthy participants remains unclear in Saudi Arabia.

OBJECTIVES: Assess the rate of subsequent infection and immunogenicity of a single dose of ChAdOx1 vaccine at 16 weeks post-vaccination in a sample of healthy and young participants.

DESIGN: Cross-sectional study

SETTING: Academic teaching hospital in Riyadh, Saudi Arabia

SUBJECTS AND METHODS: Healthy participants 18–50 years of age, who received one dose of ChAdOx1 vaccine and had no history of SARS CoV-2 infection were recruited, and blood samples were obtained 16 weeks after vaccination to assess immunogenicity using a commercially available kit.

MAIN OUTCOME MEASURES: The rate of SARS-CoV-2 infection within 16 weeks post-vaccination.

SAMPLE SIZE: 385 participants with median (IQR) age of 34 (29-38) years.

RESULTS: Eleven (2.8%) participants acquired polymerase chain reaction (PCR)-confirmed infection within 16 weeks after a single dose of ChAdOx1 vaccine (mean [SD] 42.5 [28] days post-vaccination). No hospital or intensive care unit admissions occurred among the subjects in this sample. Females were significantly over-represented in PCR-confirmed cases of SARS-CoV-2 infection, with 10 of 11 infections occurring in females (P=.006). Antibody response against anti-spike IgG were detectable in 92.7% of subjects at 16 weeks' post-vaccination. The median anti-spike IgG level after vaccination was 273.1 (IQR 107-1052 AU/mL). However, the anti-nucleocapsid IgG antibody demonstrated a sensitivity of only 20%.

CONCLUSION: A single dose of ChAdOx1 vaccine in healthy and young individuals was associated with a low, single-digit rate of PCR-confirmed infection, most of which were mild.

LIMITATIONS: Small sample size and single-center.

CONFLICT OF INTEREST: None.

Coronavirus disease 2019 (COVID-19) has spread globally since December 2019. Immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), induced either through natural infection or vaccination, has been shown to afford a degree of protection against reinfection and reduces the risk for clinically adverse outcomes.[1] The safety of adenoviral vector vaccines has been extensively studied, and adenoviral vector-based therapeutic drugs are used in clinical practice.[2] Adenoviral vector delivered antigens are known to induce both cellular and humoral immunity after a single immunization, thus permitting their use as an emergency prophylactic tool in a pandemic.[2] Furthermore, some countries have elected to delay the timing of the second dose of vaccine by 10–12 weeks in attempts to achieve >80% coverage of the population to attain relative protection against hospitalization and death related to COVID-19.[3,4] It has been established that the use of two split-dose immunizations affords a durable and long-lasting immune response.[3] However, in the event of a pandemic or limited supply, vaccination would be performed in accordance with progress in community coverage and the priority of covering immunocompromised groups of the population. The assessment of immunogenicity and efficacy after a single dose of ChAdOx1 vaccine has been studied in several countries but not in the Saudi population. As such, we aimed to evaluate the rate of subsequent symptomatic infections in young and healthy individuals up to 16 weeks after a single dose of the ChAdOx1 vaccine and to assess the antibody response, anti-spike immunoglobulin (Ig) G and anti-nucleocapsid IgG, 16 weeks after a single dose of vaccine.

SUBJECTS AND METHODS

The study population consisted of healthcare workers, and sanitary and administrative staff at King Abdullah bin Abdulaziz University Hospital (KAAUH), Riyadh, Saudi Arabia. All participants received a single dose of ChAdOx1 vaccine (Oxford University–AstraZeneca, Cambridge, United Kingdom) in February and March 2021, and blood samples were drawn 16 weeks ±7 days post-vaccination. Vaccine doses were prepared in strict accordance with manufacturer's instructions and administered to all study participants within 30 minutes of resuspension.

Eligibility criteria included that participants be healthy adults 18–50 years of age who received a single dose of ChAdOx1 vaccine and had no history of SARS CoV-2 infection. Pregnant women or individuals who received any vaccination in the previous 6 months before enrollment were excluded. The study was reviewed and approved by the KAAUH Internal Review Board (IRB) Committee. All subjects provided informed written consent to participate in the study (IRB Log Number: 21-0016).

An email describing the study purpose, eligibility criteria, and registration information to potential subjects interested in participation was sent from the Health Science Research Center in May 2021 to all KAAUH staff. If the candidate was eligible, the research team coordinated withdrawal of a blood sample. All eligible individuals who consented to participate visited the phlebotomy unit at KAAUH 16 weeks ±7 days after vaccination. Blood samples were drawn and transported to the laboratory to evaluate antibody status following vaccination.

Post-vaccination anti-spike IgG response, which reflects the response to either previous infection or vaccination, and the anti-nucleocapsid IgG assay, which represents response to previous infection were assessed using commercially available kits (SARS-CoV-2 IgG antibody test, Abbott Laboratories, Abbott Park, IL, USA). The anti-spike IgG antibody targets the spike receptor-binding domain (RBD) in serum and plasma from individuals who received the SARS-CoV-2 vaccine or who may have been infected by SARS-CoV-2. It is used as an aid in the diagnosis of SARS-CoV-2 infection in conjunction with clinical presentation and polymerase chain reaction (PCR) testing, or to evaluate the immune status of individuals using quantitative measurement of IgG antibodies against the spike RBD of SARS-CoV-2. Interpretation of the results is based on a cut-off value of 50.0 AU/mL (<50 AU/mL is negative, ≥50 AU/mL is positive).

Anti-nucleocapsid IgG assays (IgG-N) are designed to detect Ig class G (IgG) to the nucleocapsid protein of SARS-CoV-2 in serum and plasma from patients with signs and symptoms of infection and suspicion of SARS-CoV-2 infection, or in the serum and plasma of subjects who may have been infected by SARS-CoV-2. Interpretation of the results is based on an index cut-off value of 1.4 (S/C) (<1.4 is negative, ≥1.4 is positive).

The primary endpoint of the study was the proportion of subjects with PCR-confirmed SARS-CoV-2 infection between 2 and 16 weeks after receipt of the first dose of the ChAdOx1 vaccine. The severity of COVID-19 was also analyzed as a secondary endpoint. An additional secondary endpoint included the assessment of antibody response; more specifically, anti-spike IgG and anti-nucleocapsid IgG at 16 weeks post-vaccination. Severe SARS-CoV-2 infection is defined as confirmed infection with at least one of the following features: shortness of breath at rest, or respiratory distress;

evidence of shock, acute renal failure, hepatic or neurological dysfunction; admission to the intensive care unit; or death. Moderate SARS-CoV-2 infection is defined as confirmed infection with either shortness of breath with exertion, or admission to a medical unit. Finally, mild SARS-CoV-2 infection is defined as confirmed infection with one of the following features: fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, or loss of taste or smell without shortness of breath or dyspnea, and no history of admission. No infection was defined as lack of PCR-proven SARS-CoV-2 infection over the period of the study.

Categorical variables are expressed as frequency and percentage, while continuous variables are expressed as mean and standard deviation (SD), or median and interquartile range (IQR) as appropriate. Categorical variables were compared using the chi-square or Fisher exact tests as appropriate. Continuous variables were compared using the t test or Wilcoxon rank–sum test. For all analyses, differences with *P*<.05 were considered to be statistically significant. All analyses were performed using Stata version 16.1 (StataCorp; College Station, TX, USA).

RESULTS

A total of 385 participants who received the ChAdOx1 vaccine were included in the present study. The median (IQR) age at vaccination was 34 (29-38) (**Table 1**). Sex was evenly distributed across the cohort, with females comprising 50.1% (n=193) of the sample. The median (IQR) for the body mass index (BMI) was 25.7 (23.0-29.0) kg/m^2. Eleven (2.8%) PCR-confirmed infections occurred within 2 to 16 weeks after the single dose of ChAdOx1 vaccine (mean [SD] 42.5 [28] days post-vaccination). There were no statistically significant differences in age or BMI between the PCR-confirmed infection group and the remainder of the cohort. Females were significantly over-represented in PCR-confirmed SARS-CoV-2 infection after the first dose of vaccine, with 10 of 11 infections occurring in females (p = 0.006) (**Table 1**).

There was no difference in anti-spike or anti-nucleocapsid antibody levels between males and females (**Table 2**). In terms of disease severity, 81.8% (9/11) experienced mild infection and 18.1% (2/11) experienced moderate infection, with no severe infections recorded. Measurable spike antibody titers were observed in 92.7% (357/385) of participants at 16 weeks post-vaccination. All participants without titers (28/28) had negative anti-nucleocapsid results and no history of confirmed infection (**Figure 1**). For all participants, the median level of anti-spike IgG was 273.1 AU/mL (**Table 1**). Anti-spike IgG levels were significantly higher in subjects who exhibited evidence of confirmed infection post-vaccination (median 6876.6 AU/mL) compared to participants who had no evidence of confirmed infection (median 265.9 AU/mL; *P*<.0001). Titers among females and males were 267.4 and 257.8 AU/mL, respectively (*P*=.4) (**Table 2**). Antibody titer waned against nucleocapsid antigen protein in the confirmed infection group, but did not disappear completely by the end of the 16th week. Of 11 PCR-confirmed cases of infection, 7 (63.6%) were negative for nucleocapsid antigen, and 11 (100%) were positive for anti-spike IgG at 16 weeks post-vaccination. Interestingly, among those with no confirmed infection, 16 (4.2%) participants were found to be positive for nucleocapsid antigen at 16 weeks.

Table 1. Characteristics of participants at 16 weeks post single dose of ChAdOx1 vaccine among healthy adults.

Characteristic	Total sample (n=385)	PCR-confirmed infection (n=11)	No confirmed infection (n=374)	*P* value
Sex				
Female	193 (50.1)	10 (91.0)	183 (48.9)	.024
Male	192 (49.9)	1 (8.3)	191 (51)	
Age (years)	34 (29-38)	33 (31-35.5)	34 (29-38)	.3
BMI (kg/m^2)	25.7 (23-29)	23.0 (22.2- 76.4)	25.8 (23.1- 29.2)	.707
Anti-nucleocapsid IgG antibody >1.4 index	20 (5.1)	4 (36.3)	16 (4.2)	<.001
Anti-spike IgG antibody >50 AU/mL	357 (92.7)	11 (100)	346 (92.5)	.999
Anti-spike IgG antibody (AU/mL)	273 (107, 1053)	6876.6 (2656.6- 10933)	264.6 (104-936)	<.001

Data are n (%), mean (standard deviation) for age and median (interquartile range) for BMI, age, and anti-spike IgG antibody.

Table 2. Antibody response among males and females at 16 weeks post single dose of ChAdOx1 vaccine in young and healthy participants.

Characteristic	PCR-confirmed infection			No confirmed infection		
	Male (n=1)	Female (n=10)	*P* value	Male (n=191)	Female (n=183)	*P* value
Anti-nucleocapsid IgG antibody >1.4 index	0 (0)	4 (44)	<.001	10 (5.23)	6 (3.3)	.4
Anti-spike IgG antibody >50 AU/mL	1 (100)	10 (100)	.999	177 (92.7)	168 (92.3)	.75
Anti-spike IgG antibody (AU/mL)	2011	6876.6 (2656.6-12266.5)	.999	267.4 (99.8-2704.7)	257.8 (105-566)	.69

Data are n (%) and median (interquartile range) for Anti-spike IgG antibody.

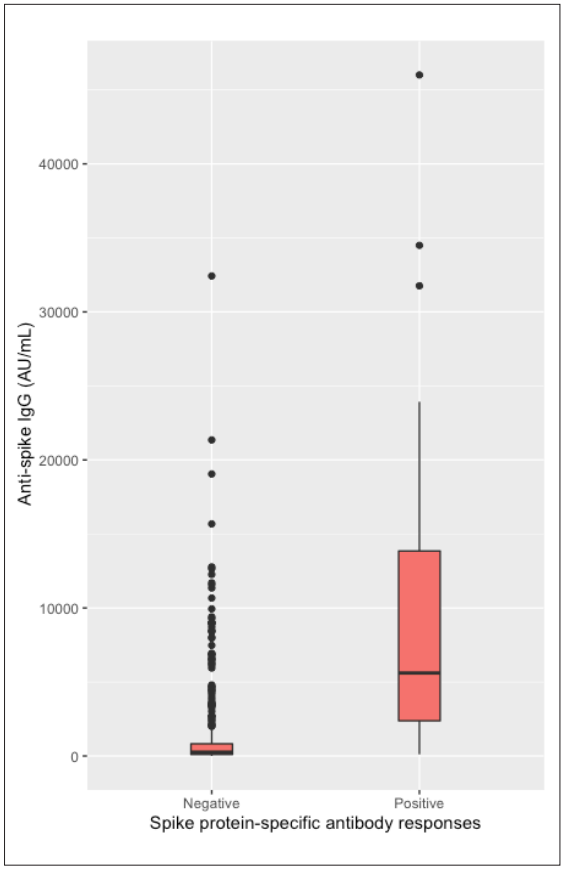

Figure 1. Spike protein-specific antibody responses in infection and non-infection subjects 16 weeks after single dose vaccination with ChAdOx1 vaccine (median, interquartile range).

DISCUSSION

A two dose-regimen of ChAdOx1 vaccination has been investigated and found to be safe and effective against SARS-CoV-2 infection, with 95% vaccine efficacy.[5] Here, we assessed the efficacy of a single dose of ChAdOx1 vaccine among a sample of young and healthy individuals in Saudi Arabia. Our results revealed that a single dose was associated with a substantially reduced risk for PCR-confirmed SARS-CoV-2 infection (2.8%) over a 16-week period. Across the entire cohort, there was no mortality nor severe COVID-19 illness. This result reflects the impact of vaccination in our population; measurable spike antibody titers were evident in >92% of the entire cohort at 16 weeks after a single dose of vaccine, with median antibody titers of 265.[9] AU/mL for infection-naïve participants. This is somewhat higher than reported among young individuals after a single dose in other countries.[7,8] However, this corroborates the earlier finding that a single dose of ChAdOx1 produces such a protective titer and led to a very low PCR-confirmed infection rate within the first 16 weeks post-vaccination.

Results of the present study revealed that in individuals who acquired PCR-confirmed infection after vaccination, females exhibited a higher probability of being infected compared to males (91% versus 9%, respectively); however, there was no statistically significant difference in anti-spike antibody or anti-nucleocapsid antibody results between the sexes at 16 weeks post-vaccination. A United Kingdom study involving 3610 healthcare workers with a median age of 41 years did not find an association between sex and single-dose ChAdOx1 vaccine antibody responses.[10] In contrast, a previous study reported that females generated stronger humoral immunity and greater vaccine efficacy than males.[6,9,11] One study involving 4800 participants reported that antibody levels wane rapidly after two doses of

the BNT162b2 vaccine, especially among males, those ≥65 years of age, and immunocompromised patients.[13] Among our population, it is plausible that females sought medical attention at a higher rate than males, or that both sexes generated the same humoral immunity, but females were more prone to acquire SARS-CoV-2 infection.

In the PCR-confirmed infection group, 7 (63.6%) of the serum samples were negative for anti-nucleocapsid IgG at 16 weeks post-vaccination, whereas a similar study found a higher percentage of anti-nucleocapsid negativity (36%) after 14 weeks following SARS-CoV-2 infection. However, the seronegative cases were significantly higher in the younger population. This may suggest that the waning of anti-nucleocapsid antibodies may occur faster among younger individuals who acquire asymptomatic infection.[12] Interestingly, of 11 PCR-confirmed participants, only 4 had a seropositive anti-nucleocapsid IgG titer. This reflects the poor performance of this test, with a sensitivity of only 20%. Furthermore, 16 participants among the uninfected group of 374 participants had a seropositive titer to anti-nucleocapsid IgG. It is not possible to determine whether these patients developed asymptomatic infection post-vaccination or before vaccination, or simply had false-positive results.

In conclusion, our results suggest that a single dose vaccination offered ample protection against serious COVID-19 in a young and healthy population in Saudi Arabia compared to other countries. Females were more prone to infections compared to males after vaccination. However, anti-nucleocapsid IgG antibody demonstrated little utility in clinical practice. Limitations of the present study include its small sample size, single-center design, lack of neutralization assays, and lack of weekly PCR or antigen testing to assess the actual rate of infection among asymptomatic participants. However, from an ethical perspective, such testing would have been prohibitive due to its burden on the participants.

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