

# Safety, Tolerability and Immunogenicity of Oxford-AstraZeneca ChAdOx1 Vaccine Among Polish School-Teachers

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## Research Article

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# Abstract

## Background

Polish teachers, as the priority group, were offered the ChAdOx1-S vaccine since February 2021. The objective was to investigate safety, tolerability and immunogenicity of this vaccine following two vaccine doses.

## Methods

Teachers were invited for serological testing  $\geq 8$  weeks after second vaccination. Quantitative post-vaccination anti-spike antibody responses were measured using the Abbott SARS-CoV-2 IgG II Quant assay (detection threshold:  $\geq 7.1$  BAU/ml). Multivariable logistic regression methods were used to identify predictors of immunogenicity.

## Results

Of 192 teachers, mean age  $50.5 \pm 8.3$  years, 83.9% were females. Median (range) dosing interval was 50 (14-95) days; median interval between the second dose and immunogenicity test was 69 days (range: 57–111). More than a half of teachers (58.3%) reported they would change the product for another (mostly mRNA) vaccine if there was such an opportunity. Adverse reactions after receiving the vaccine (either the first or the second dose) were reported by 79.2% teachers, more frequently after the first dose (84.9%), and were similar in nature to those previously reported: feeling feverish (44.8%), headache (41.7%), malaise, chills (both: 38.0%), injection-site tenderness (37.5%) and pain (32.3%). Less males than females (54.8% vs 80.1%) and older (aged  $\geq 50$  years) than younger teachers (65.7% vs 90.4%) reported side effects ( $p < 0.002$ ;  $p < 0.0001$ , respectively). By  $\geq 8$  weeks after the boost dose, all teachers had neutralizing antibody responses. The median (range) anti-spike IgG reading was 525.0 BAU/mL (20.6–5680.0 BAU/mL); 1008.02 (115.3–5680.0) BAU/mL in teachers with evidence of prior infection and 381.42 BAU/mL (20.6–3108.8) in those without ( $p = 0.001$ ). Previous infection with SARS-CoV-2 and longer dose interval were both positive predictors of higher immunologic response ( $p < 0.0001$ ;  $p = 0.01$ , respectively), with no evidence of differences by age, gender, BMI, smoking or comorbidities.

## Conclusions

The results demonstrated good safety, tolerability and immunogenicity of the ChAdOx1-S vaccine. Immunization led to detectable anti-spike antibodies in all teachers. Our study justifies the longer dose interval as an important factor to enhance higher antibody response. Findings suggest that in immunocompetent vaccine recipients with an evidence of previous infection a delay regarding the second dose could be considered when careful management in the use of vaccine resources is needed.

# Background

Multiple COVID-19 (coronavirus disease 2019) vaccines have been developed globally as the most effective preventive method to combat SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) pandemic [1]. Poland, as other European Union (EU) countries, started its National COVID-19 Vaccination Program on December 27th 2020, with the introduction of the Pfizer-BioNTech BNT162b2 vaccine as the first product approved for the EU market. The vaccine regimen was gradually expanded, with three other vaccines approved currently for use: Moderna mRNA-1273, Oxford-AstraZeneca ChAdOx1 nCoV-19 and Johnson and Johnson/Jansen Ad26.COV2.S [2].

COVID-19 vaccinations have been rolled out through various phases. In the first phase, all EU/EEA countries started vaccinating the priority groups, which were selected based on their higher risk of developing severe disease, as well as healthcare and other front-line workers. Poland primarily prioritized elderly people (80 years old and above), residents and personnel in long-term care facilities, healthcare workers, and essential public service workers, such as educational institution workers [2, 3]. Of note, Poland was one of the first countries to recommend the vaccination of teachers in accordance with UNESCO (The United Nations Educational, Scientific and Cultural Organization) recommendation [4].

Since February 12th 2021, ChAdOx1 nCoV-19 vaccine has been provided to voluntarily immunize Polish teachers [5]. The vaccine uses an adenovirus vector of a chimpanzee. The genetic sequences contained in the adenovirus encode the synthesis of the SARS-CoV-2 coronavirus surface protein S. As a result, the vaccine induces a specific immune response to the coronavirus surface protein S [6]. Higher S-binding antibodies were observed with increasing dose interval [7,8]. In Poland, the vaccination schedule has been initially adopted in accordance with the recommendations of the producer, with two doses of the vaccine administered with an interval of 10-12 weeks [6]. On May 17th 2021, following to the governmental regulation, between-doses interval was reduced to 35 days [9].

Governmental recommendations to limit vaccine provision among Polish teachers to only ChAdOx1 nCoV-19 was met with a wave of criticism and dissatisfaction, as the offer was perceived as 'worse' than compared to mRNA (messenger ribonucleic acid) vaccines. Regarding the teachers' doubts related to the product, the most common argument was its questionable effectiveness [5,10]. Additionally, reducing between-doses interval, which was not evidence based, left some potential recipients confused and arose questions around its impact on the vaccine immunogenicity. There were also concerns about the emerging reports of its side effects, such as flu-like symptoms, accompanied by high fever and muscle pain, as well as blood clots listed as very rare side effects of the vaccine [11,12].

Universal teacher immunization remains crucial in order to ensure continuity of education. To achieve this, it is necessary to build vaccine trust among this professional group through wide-ranging information campaigns, as well as continuous scientific research to better determine the safety, tolerability, effectiveness and immunogenicity of COVID-19 vaccines.

Mild or moderate local and systemic reactions to the ChAdOx1 nCoV-19 vaccination were reported in numerous randomized control trials (RCTs) [7,13-16]. For instance, in the report of the phase 2 of a single-blind RCT on the ChAdOx1 nCoV-19 vaccine delivered by Ramasamy et al. local and systemic reactions were more common in participants given the vaccine than in those given the control, meningococcal vaccine [13]. However, there is presently limited information available outside RCTs regarding the safety and tolerability of ChAdOx1 nCoV-19 vaccine [17,18].

The assessment of vaccine-generated immune responses to SARS-CoV-2 spike antigens, has mostly focused on the development of antibodies targeting the S1 domain of the viral spike protein. Anti-spike antibody titres, associated with neutralizing activity, provide a potential surrogate marker of protection [14,19-21]. A key benefit of vaccine regimens is that anti-S IgG titres are higher than for natural infection. More than 99% of boosted participants of the RCT had neutralizing antibody responses by 14 days after the second dose [13]. Eyre et al. also reported that vaccination with the ChAdOx1 nCoV-19 vaccine led to detectable anti-spike antibodies in nearly all adult HCWs [20]. Immunogenicity data for the vaccine, reported from the community trials, are rather scant.

Understanding the time-dependent dynamics of post-vaccine anti-spike antibody measurements, and assessing how they differ between individuals e.g., by age, gender, body mass index (BMI), comorbidities etc. is also increasingly important; however, not much information is currently available regarding ChAdOx1 nCoV-19 vaccine [7,13,18,20].

Considering the important need of real-life data on safety, tolerability and immunogenicity data for the ChAdOx1 nCoV-19 vaccine and being concerned that such data have not been assessed yet in Polish population, we decided to assess reported adverse events following immunization, as well as to measure anti-spike IgG responses in teachers following two vaccine doses. How responses vary between those with and without previous evidence of infection, as well as other determinants of SARS-CoV-2 anti-spike IgG responses have also been evaluated.

## Methods

### Population and Setting

Post-vaccine antibody responses were studied between June-July 2021 in consecutive teachers recruited from primary, secondary and high-schools through local teacher networks. Convenience sampling design was adapted to recruit teachers with a goal of 200 participants. All schools were located in the capitals of 2 Polish provinces: Zielona Gora and Szczecin. Inclusion criteria were as follows: employed as a teacher; being immunized with 2 doses of the ChAdOx1 nCoV-19 vaccine at least 8 weeks before the survey. Teachers contacted the research team directly via a dedicated phone line if they wanted to participate. Following initial contact with the study team, participants were then informed about the phlebotomy time and the health care facility address. At the phlebotomy time point, the participant information sheet was given to each teacher and written consent was then obtained.

## Study instrument

The short questionnaire was developed by the authors after intensive literature research [7,13,17,18,20] and then given to the participants before the phlebotomy. The questions concerned sociodemographic data: age, gender, school location, and core health risk factors (body-mass index [BMI], smoking status, and presence of comorbidities, including type 2 diabetes, cancer, heart/lung/ kidney disease).

Participants were then asked to record the date of ChAdOx1 nCoV-19 vaccine administration and dosing interval; this was then checked by a research team member in the national COVID-19 vaccination data base. Teachers were also asked whether they had experienced adverse effects, including both systemic and local effects. Systemic side-effects included symptoms such as: fatigue, malaise, headache, chills, fever, arthralgia, myalgia, nausea and diarrhea; local side-effects included injection site pain, tenderness, redness and swelling [7,13]. Participants could also tick “no symptoms”. Data on previous SARS-CoV-2 infection were available for the research team from the national patients’ data base after logging in. Due to the fact that some patients did not test themselves for SARS-CoV-2 infection despite medical history of COVID-19 like symptoms and/or contacts with infected patients, the information of previous infection reported by participants in the study questionnaires was taken into account while assessing individuals previously infected with SARS-CoV-2.

## Laboratory assays

Blood samples were collected by a qualified nurse/physician. Samples (5 mL) were centrifugated (15 min/4500 r. p. m.), stored at 4-8°C and then transported to the *Synevo* laboratory in Cracow, Poland where they were tested. Briefly, post vaccination anti-spike IgG responses were assessed using the Abbott SARS-CoV-2 IgG II Quant antibody assay, an automated, two-step chemiluminescent micro-particle immunoassay (CMIA), targeting the spike receptor binding domain (RBD). The assay is used for the qualitative and quantitative determination of IgG antibodies to SARS-CoV-2 in human serum and plasma on the ARCHITECT i System. The assay cut-off is  $\geq 7.1$  binding antibody units/ml (BAU/ml) reported by the manufacturer. The sensitivity (based on  $\geq 14$ -day post-positive reverse transcription-PCR samples) and specificity of the Abbott anti-nucleocapsid assay has been previously evaluated as 98.3% (90.6–100.0%) and 99.5% (97.1–100%), respectively [22].

Each study participant was given a code number, placed both on the questionnaire and on a test tube. From July 11th 2021, teachers were able to obtain information about their vaccination serological test results.

## Vaccination immunogenicity assessment

On the basis of the results obtained after sero-testing, relevant parameters were calculated to assess the immunogenicity of the ChAdOx1-S vaccine. The following parameters were evaluated:

- GMT (geometric mean titers) calculated at  $\geq 2$  weeks after vaccination,
- PR (protection rate) – the proportion of subjects with an IgG antibody titer  $\geq 7.1$  BAU/ml.

## Statistical analysis

Data were analyzed using a customized program STATISTI-CA PL, Version 12.5 (StatSoft, Cracow, Poland, 2016). Categorical data were presented as frequencies with percentages and continuous data as means and ranges. Teachers were grouped into those with evidence of prior infection (i.e. those who reported having any positive anti-spike or anti-nucleocapsid antibody test or positive PCR prior to first/second vaccination and those who reported having COVID-19 without confirmation by any diagnostic test) and those without (including participants with no previous serology or PCR testing). Categorical variables were compared by the chi square test, while continuous variables were compared by a Student's t-test. Correlations were calculated using standard Pearson's correlation. The occurrence of adverse effects was studied for the first and the second dose of ChAdOx1 n CoV-19 vaccine. To assess determinants of the occurrence of adverse effects we used the following strata: age ( $\leq 55$  years vs  $>55$  years), gender, teacher status regarding previous SARS-CoV-2 infection (binary variable), obesity (BMI  $<30$  kg/m<sup>2</sup> vs  $\geq 30$  kg/m<sup>2</sup>), and comorbidities (binary variable, with/without comorbidities).

Proportions of anti-spike positive teachers were estimated by checking anti-spike IgG antibody titer at least 8 weeks post-second vaccination. The primary endpoints, anti-spike IgG antibody titer and seroprotection rate, were analyzed. Positive anti-spike IgG antibody titers were analyzed using geometric mean titer (GMT). Multiple linear regression was applied to determine the predictors of immuno-genicity measured by anti-S antibody titers  $\geq 8$  weeks post-second vaccination. We modelled quantitative IgG antibody titres using several multi-variable logistic regression models, and fitting separate models by prior infection status. All models were reduced by the use of the stepwise backward elimination method [23]. Non standardized regression coefficients in the regression model were used to evaluate any changes in the model. Regression results are presented together with 95% confidence intervals (CIs). A p-value was statistically significant if  $\leq 0.05$ .

## Results

Overall, 200 teachers were invited to participate of whom 8 were disqualified due to the misinformation regarding their vaccination status. Finally, 192 teachers were tested for anti-spike SARS-CoV-2 IgG. Their demographic details and the SARS-CoV-2 infection status prior to immunization are given in Table 1.

Table 1

Demographics of teachers who received a second dose of ChAdOx1 n CoV-19 vaccine; Poland, 2021, n=192.

Variable	n	%
Gender		
Female	161	83.9
Male	31	16.1
Age (years):* 50.5 (27–67)		
27-40 years	17	8.9
41-50 years	73	38.0
>50 years	102	53.1
BMI kg/m <sup>2</sup>		
< 25	90	49.2
25.0-29.9	69	37.7
≥ 30	23	13.1
Smoking		
current	23	12.0
quit	26	13.5
never	143	74.5
Comorbidity		
Cardiovascular disease	13	6.8
Respiratory disease	8	4.2
Diabetes	19	9.9
Other**	47	24.5
No comorbidity	105	54.6
Previous SARS-CoV-2 infection		

\*Mean (range)

\*\*\*rheumatoid arthritis, chronic liver disease, cancer, taking corticosteroids, taking immunosuppressants

\*\*\* PCR/antigen/serologic test

Variable	n	%
Assessed by the test***	27	14.1
Assessed by the participant	22	11.4
No infection	143	74.5
*Mean (range)		
***rheumatoid arthritis, chronic liver disease, cancer, taking corticosteroids, taking immunosuppressants		
*** PCR/antigen/serologic test		

Mean age of participants was 50.5 years, standard deviation (SD) 8.3, range: 27–67 years; 16.1% were males. Regarding BMI, 38% were overweight, and 13% were obese. Smoking at the time of vaccination and/or in the past was declared by 12% participants and 75% declared that they had never smoked. Almost a half of teachers (45.4%) reported comorbidities, mainly diabetes (10%), followed by cardiovascular disease (7%). Previous SARS-CoV-2 infection was reported by 49 (25.5%) of participants, of those - in 27 (55.1%) an infection was confirmed by a PCR/antigen test, in the rest – an infection was reported by a participant with the medical history of COVID-19, however, this was not confirmed by any test.

More than a half of teachers (112/192; 58.3%) reported they would change the product for another vaccine if there was such an opportunity, 16.1% would not, 25.5% were not sure. A mRNA vaccine was the most common option (Pfizer-BioNTech BNT162b2 Comirnaty: 88.4% and Moderna mRNA-1273 Spikevax: 7.1%), another vector vaccine - Janssen COVID-19 Ad26.Cov-2.S vaccine was the rarest choice (2.5%).

## Adverse effects

Any local and/or systemic reaction after receiving the first or the second dose was reported by 152/192 (79.2%) of teachers; of those 129 teachers reported adverse effects as more expressed after the first dose, 6 - after the second dose; 10 – the same after the first and the second dose, 7 participants were not sure. Among vaccinated teachers, 103 (53.6%) reported one or more local adverse effects and 140 (72.9%) indicated having one or more systemic adverse effect. The most common local reaction after receiving the vaccine was tenderness at the injection site (37.5%) followed by feeling injection-site pain (32.3%). When looking at the number of reports on systemic side effects, the most common were: feeling feverish (44.8%), followed by headache (41.7%), malaise, chills (both: 38.0%) and fatigue (36.5%); Fig. 1.

Women were more likely to report adverse effects than men (129/161; 80.1% vs 17/31; 54.8%,  $p < 0.002$ ). Local and systemic reactions were more common in teachers aged <50 years than older teachers (75/83; 90.4% vs 71/108; 65.7%,  $p < 0.0001$ ). The difference between the proportion of teachers having side effects and previously infected with SARS-CoV-2 and those not infected was not significant (35/50, 79.5% vs 111/151, 75.5%;  $p = 0.58$ ).

## Median dosing interval

Median (range) dosing interval was 50 (14-95) days; time between the second dose and a serological test was 69 days (range: 57–111 days).

## Antibody response

By  $\geq 8$  weeks after the second dose, all boosted teachers had neutralizing antibody responses. Median anti-spike SARS-CoV-2 IgG for the total of 192 participants was 525.0 BAU/mL (20.6-5680.0 BAU/mL). In eight (4.2%) participants (5 males and 3 females, age range: 43-66 years, BMI range: 22.7-30.2 kg/m<sup>2</sup>, of whom 2 reported comorbidities and none reported previous infection) the anti-spike IgG reading was below 50.0 BAU/mL (range: 20.6-43.5).

As expected, those with previous infection developed substantially higher titres of anti-spike IgG. The median (range) anti-spike IgG reading  $\geq 8$  weeks post second vaccine dose was 1008.02 (115.3–5680.0) BAU/mL in teachers with evidence of prior infection and 381.42 BAU/mL (20.6–3108.8) in those without an infection ( $p=0.001$ ). Figure 2 illustrates antibody responses among 192 teachers following second vaccination with ChAdOx1 by prior infection. Data are shown as a bar chart of a total cohort where teachers with previous SARS-CoV-2 infection are shown in red on the bar chart (A) and as a box plot which displays the median values (B), with the interquartile range and  $\pm 1.5$ -fold the interquartile range from the first and third quartile (lower and upper whiskers).

## Correlation of rate of anti-S antibody titres and selected variables

A statistically significant correlation was observed between dose interval (Pearson's product-moment correlation  $r$  0.207, 95% CI: 0.065 and 0.341,  $p=0.006$ ), days between receiving the second dose and performing the serological test ( $r$  -0.198, 95% CI: -0.322 and -0.048;  $p=0.009$ ) and age ( $r$  0.144, 95% CI: 0.002 and 0.280;  $p=0.046$ ) with anti-S antibody titres, respectively.

Table 2 presents anti-ChAdOx1 neutralizing titres after the second dose of vaccine by selected variables in previously uninfected and infected teachers. Data are shown as bar chart of a total cohort where teachers with previous natural SARS-CoV-2 infection are shown in red on the bar chart (A) and as a box plot which displays the median values (B), with the interquartile range and  $\pm 1.5$ -fold the interquartile range from the first and third quartile (lower and upper whiskers).

Table 2  
Anti-ChAdOx1 neutralizing titres after the second dose of vaccine by selected variables in previously uninfected and infected teachers.

Variable	Previously uninfected			Previously infected with SARS-CoV-2		
	GMT	N	p	GMT	N	p
Gender						
Female	347.7	121	0.51	1048.1	41	0.89
Male	413.2	24		984.7	7	
Age (years)						
< 40	355.7	13	0.95	741.8	4	0.0001
40-60	347.3	120		862.5	39	
≥ 60	473.2	12		3053.6	4	
BMI						
< 25 kg/m <sup>2</sup>	336.5	67	0.86	803.5	24	0.04
≥ 25 - 29.9 kg/m <sup>2</sup>	350.0	57		866.1	15	
≥ 30 kg/m <sup>2</sup>	462.7	15		1666.1	6	
Comorbidities*						
Yes	335.1	98	0.57	833.3	35	0.52
No	383.7	39		1150.1	7	
Current/Previous smoker						
Yes	440.5	19	0.37	942.3	36	0.30
No	536.6	128		1354.2	11	
*rheumatoid arthritis, chronic liver disease, cancer, taking immunosuppressants, corticosteroids						

Regarding previously uninfected teachers, and teachers infected with SARS-Cov-2 no statistically significant differences were observed concerning gender (p=0.51 and p=0.89 respectively), comorbidities (p=0.57 and p=0.52 respectively), smoking status (p=0.37 and p=0.30 respectively) and anti-spike IgG titers. Significantly higher anti-spike IgG titers were reported among older teachers (≥ 60 years) with previous SARS-CoV-2 infection compared to younger ones (p<0.0001) and among those obese (≥ 30 kg/m<sup>2</sup>) compared to those who reported BMI<30 kg/m<sup>2</sup> (p=0.04). Among previously uninfected teachers there were no statistically significant differences regarding age (p=0.95) and BMI (p=0.86) and anti-spike IgG titers.

# Predictors of immunogenicity

Multiple logistic-regression analysis regarding an association of immunogenicity (measured by the level of anti-spike IgG titers) with selected variables revealed that previous infection with SARS-CoV-2 and longer dose interval were independent positive predictors of higher immunologic response ( $p < 0.0001$  and  $p = 0.01$  respectively); Table 3.

Table 3

Logistic-regression model\*: association of anti-spike IgG titers with selected variables: estimates, 95% confidence intervals (CIs) and p values;  $n = 192$ .

Variable	Estimate	95% CI	p
Intercept	-1173.84	-2161.24 -186.45	0.02
Age	10.83	-1.79 – 23.64	0.09
SARS-CoV-2 infection: yes	545.17	300.69– 798.64	<0.0001
Dose interval	14.31	3.43– 25.20	0.01
*Multiple R-squared: 0.170, Adjusted R-squared: 0.154			

## Discussion

### Results overview

In the present survey we sought to better understand the safety, tolerability and immunogenicity of the ChAdOx1 nCoV-19 vaccine among Polish teachers. Interestingly, two out of three teachers reported they would change the product for another vaccine – mostly a mRNA vaccine - if there was such an opportunity; this clearly highlights the necessity of this study.

The vast majority of teachers receiving ChAdOx1 nCoV-19 experienced more than one side effect at the same time. Adverse events were significantly more common after the first dose and were mild in severity. Injection site pain was the most common type of local side effects. Common systemic symptoms were: feverishness, followed by headache, malaise fatigue and chills. Reactions were significantly less common in males and in older teachers.

In this cohort of teachers, predominantly healthy adults of working age, all developed a positive anti-spike IgG antibody test by  $\geq 8$  weeks post vaccination. Mean GMTs remained relatively high in all age groups.

Previous infection with SARS-CoV-2 and longer dose interval were both positive predictors of higher immunologic response.

## Median dosing interval

Median dosing interval in this study was 69 days, with the range of 25-111 days; only two teachers reported a shortened interval between ChAdOx1 doses. This means that the vast majority of the study participants did not follow the Polish government recommendation, announced on May 17th 2021, which endorsed 35 days as a between-doses interval [5]. It is worth emphasizing that this regulation was in opposite to the United Kingdom (UK) and several other countries policy to employ an 'extended interval' vaccine regimen in which the booster dose of ChAdOx1 vaccine is delayed for 10 to 12 weeks following the first dose [6,24].

## Frequencies and intensity of adverse reactions

We found that any systemic adverse effects affected almost three in four participants and local side effects – more than every second teacher. Very similar results regarding systemic solicited adverse events (71.6%) were reported in the double-blind, randomized, placebo-controlled, phase 3 clinical trial on ChAdOx1 nCoV-19 vaccine, conducted in the United States, Chile, and Peru [16]. However, more participants in the RCT group than in our study had local solicited adverse events (74.1%). The reactogenicity of the ChAdOx1 nCoV-19 vaccine in teachers up to 67 years of age was also comparable to that reported in other RCTs [7,13-15] and listed in the product characteristics [6], as well as to observed by some other authors who conducted research outside clinical trials [17,18].

Furthermore, adverse effects observed in this study were similar in nature to those previously reported (feeling feverish, headache, malaise, chills, injection-site tenderness and pain) [13,16,17]. Severe systemic allergic reactions following immunization, such as anaphylactic shock, were not reported by study participants, however, the small sample size reduced the chance to detect such adverse events. Recent data imply an incidence of anaphylactic shock as very infrequent (1 per 200,000 -1 per million doses) [25].

We found fewer adverse events among the studied teachers after the boost vaccination than after the prime vaccination. Similar results have been seen in other studies which assessed the ChAdOx1 nCoV-19 vaccine safety [13,16,17]. Of note, some other studies found that individuals vaccinated with the ChAdOx1 nCoV-19 vaccine were more likely to experience systemic side-effects than those who had been given the BNT162b2 vaccine [26].

Side-effects were more prevalent in teachers aged <50 years than older teachers. Our results provide evidence to support other studies, both the RCTs and conducted in the community, of lower occurrence of

side-effects in older than in younger individuals [13,16,17,26]. We also found that adverse effects were less common in men than women which is consistent with previous studies [17].

Local and systemic side effects were reported to be higher in individuals previously infected with SARS-CoV-2 than in those without known past infection for BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccines [17,27-29]. Given evidence from these studies, we investigated the extent to which previous SARS-CoV-2 infection was associated with reports of adverse effects. No consistent difference in occurrence of systemic/local adverse effects between individuals who reported a previous infection and those who did not might be due to the small sample size, as well as to the information bias; although in 55% of teachers SARS-CoV-2 infection was confirmed by an adequate test, in the rest of cases the analyses relied on participants reports regarding previous infection.

## Anti-spike antibody titres

We found 100% seroconversion rate among the study population after receiving two doses of ChAdOx1 vaccine, however, 4.2% of participants were low responders. As such, these findings show that vaccination is highly effective for induction of spike-specific immune responses in the working-age population, such as teachers. Some other studies reported similar rates of low responses among participants, however, in contrast with our results, this was independently associated with several long-term health conditions [18].

Antibody levels after two vaccine doses were significantly higher in individuals with prior SARS-CoV-2 infection compared to those achieved by teachers without infection. Previous infection with SARS-CoV-2 was the biggest positive predictor of the magnitude of quantitative antibody response post second vaccine dose, with median readings 2.6-fold higher with previous infection compared to without infection. This was also reported by other authors who explored this trend regarding ChAdOx1 nCoV-19 vaccine [7,18], as well as other vaccines [18,30-32]. For instance, a study conducted among Israeli healthcare workers (21 days post-dose 1 of the BNT162b2 mRNA COVID-19 vaccine) found that those with prior infection had antibody titres one magnitude order higher than naïve individuals [29]. These findings may suggest prioritization on uninfected persons in regions where COVID-19 vaccine-sparing strategies are required [31,32]; such prioritization may also refer to the third vaccination in previously infected healthy individuals.

Concerning our second main finding, longer dose interval led to a greater immune response to ChAdOx1 nCoV-19 vaccine. Other studies confirmed that dosing interval is one of the most significant factor in determining the efficacy of this vaccine [7,8]. For instance, an analysis of four RCTs, conducted in South Africa, Brazil and the UK, found that efficacy was higher if the booster ChAdOx1 nCoV-19 vaccine dose was received 8-11 weeks after the first; furthermore, it was increased if participants received the booster dose more than 11 weeks after the first [7]. This incremental VE with increasing prime-boost intervals positively correlated with GMTs of anti-SARS-CoV2 spike IgG binding antibody. A similar boost to

antibody responses was seen with a longer duration in some other studies on the BNT162b2 COVID-19 vaccine [21,33].

Among demographic factors, older age has been repeatedly reported to associate with reduced antibody responses after COVID-19 vaccination due to age-related decline in immune functions [18, 34]. No statistically significant differences in the antibody response between age groups were found in this survey, possibly due to a defined study population, i.e. teachers in a relatively young age (median of 50.5 years). However, a relatively low correlation was found between age ( $r = 0.144$ ,  $p = 0.046$ ) with anti-S antibody titres. Some studies found [7,13,21] that two vaccine doses achieved high responses across all age groups, which supports our findings. By contrast, another two-dose mRNA vaccine candidates have shown immunogenicity in older adults, but absolute neutralizing antibody responses in adults aged 65–85 years were lower than in those aged 18–55 years [35]. A two-dose inactivated virus vaccine has also shown lower absolute neutralizing antibody titres in adults aged 60 years and older than in adults aged 18–59 years [36]. Additional studies on post-vaccination antibody responses in different age groups would be of value.

In our survey of teachers no association was found between female gender and better ChAdOx1 vaccine antibody response. This may be due to the small sample size and relatively small representation of males in the sample, as well as to the fact that the study population consisted of the middle-age individuals. Some previous studies found that between-gender differences in antibody responses become more marked above 60 years of age [20]. Our findings are consistent with some previous observations [21], however, other authors which conducted larger population studies reported that females generate stronger humoral immunity than males [18,37].

Although many long-term health conditions, such as rheumatoid arthritis, chronic liver disease, type 2 diabetes, obesity, asthma, hypertension, as well as taking corticosteroids and immunosuppressants were independently associated with low responses [18,38], we did not detect any significant differences in antibody responses regarding teachers with comorbidities and healthy individuals. This may be attributable to the relatively low fraction of teachers reporting any long-term health conditions.

## Limitations

Potential limitations did exist in this study. The sample size of our study population was relatively small, which could possibly hinder some of the associations. Second, our cohort was predominately females. This echoes the demographic profile of Polish teachers with males comprising only 17.8% [39]. However, for the gender-discrepancy reason, the cohort may not be representative for the entire population of working adults. Third, self-reported data were used for variables such as BMI and comorbidities, as well as (in 45% of participants) regarding the previous SARS-CoV-2 infection. This can introduce information bias, together with misclassification. The time of evaluation ranged between 1 and 4 weeks following the second immunization, introducing time as a possible bias. However, when the evaluations were controlled for this factor, they still yielded the same results. Furthermore, we assessed the intensity of the overall

side-effects following the ChAdOx1 nCoV-19 immunization, no matter which dose had been taken. Although the vast majority of participants reported adverse events as more intense after the first vaccination than after the second one, the frequency assessed in this study could have been slightly higher than while assessed separately for each dose of the vaccine. Furthermore, T-cell response was not assessed in this study. Although the correlation between antibody response and vaccine efficacy is high, which suggests that the neutralizing antibody response is important, T-cell responses may contribute to protection from COVID-19 even in the presence of lower neutralizing antibody titers [20]. Finally, the study design (a cross-sectional study) does not allow an inference of causality [17].

## Conclusions

While robust conclusions from the survey results are limited due to the small sample size, this report demonstrates that the ChAdOx1 nCoV-19 vaccine appears safe, well tolerated and immunogenic in the studied population of teachers. Although mild adverse effects affected the majority of teachers, more commonly after the first dose, immunization led to detectable anti-spike antibodies in all teachers. Significantly higher immunogenicity was observed in participants who reported previous SARS-CoV-2 infection. The latter finding suggests that in immunocompetent vaccine recipients with an evidence of previous infection a delay regarding the second dose could be considered any time when careful management in the use of vaccine resources is needed. Further large-scale studies are urgently required to better assess the duration of antibody responses regarding the ChAdOx1 nCoV-19 vaccine.

The timing between priming and boosting has emerged as a critical aspect of the COVID-19 vaccination programs. Our study justifies the longer dose interval as an important factor to enhance higher antibody response post ChAdOx1 nCoV-19 vaccination.

The results may help to remove the odium, commonly expressed by the Polish teachers, of ChAdOx1 nCoV-19 vaccine being “the worse” product. The findings may also encourage general practitioners, nurses and other healthcare providers involved in immunization process, to promote the ChAdOx1 nCoV-19 vaccination among other patients. This is particularly important as the ChAdOx1 nCoV-19 vaccine is likely to be one of the least expensive among of all the currently authorized Covid-19 vaccines. Notably, further investigation on the effectiveness of the ChAdOx1 nCoV-19 vaccine need to be made in the context of the currently circulating variants of interest and variants of concern and the possible evolution of other SARS-CoV-2 lineages.

## Abbreviations

**anti-S IgG:** *anti-spike Immunoglobulin G*

**BAU:** **binding antibody units**

**BMI:** **body mass index**

**CI:** Confidence interval

**COVID-19:** Coronavirus disease 2019

**EU:** European Union

**GMT:** Geometric mean titers

**mRNA:** messenger ribonucleic acid

**PCR:** Polymearase Chain Reaction

**PR:** Protection rate

**RCTs:** Randomized control trials

**SD:** *Standard deviation*

**SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2

**UK:** *United Kingdom*

**UNESCO:** United Nations Educational, Scientific and Cultural Organization

**WHO:** World Health Organization

## Declarations

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### Availability of data

The datasets generated and/or analyzed during this study contain clinical data and are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Informed written consent was obtained from all teachers included in the study. The project received consent from the Bioethical Committee of Collegium Medicum of the University of Zielona Gora (KB-UZ-9/21). Confidentiality was ensured throughout the study.

## Competing interests

The authors have no competing interests.

## Consent for publication

Not applicable.

## Authors' contributions

M.G. designed and planned the study, searched the literature, was responsible for funding acquisition, wrote the draft and critically reviewed the manuscript. E.S., J.G. and D.B. performed the field work and collected the data. M.K., D.B., E.S., J.G. and O.P. analyzed the data and O.P. prepared figures. All authors reviewed the manuscript.

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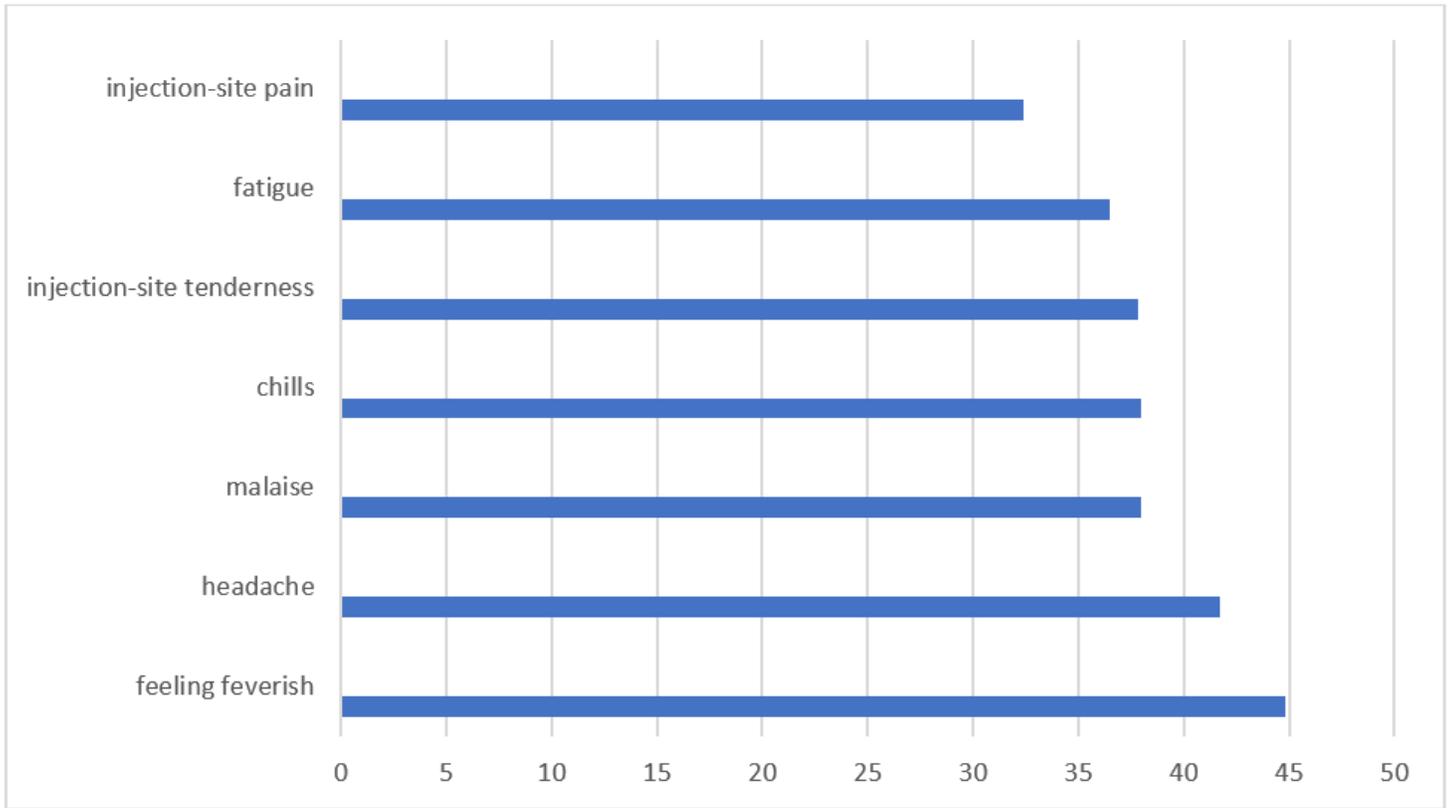
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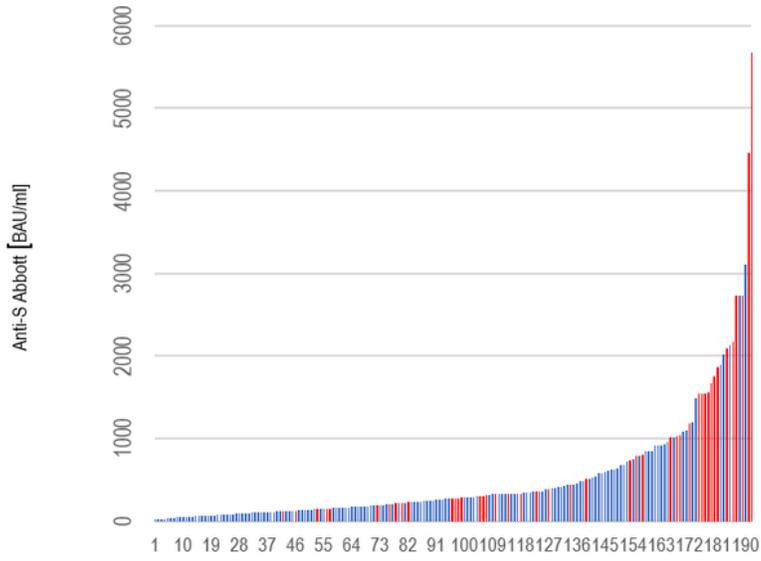
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## Figures

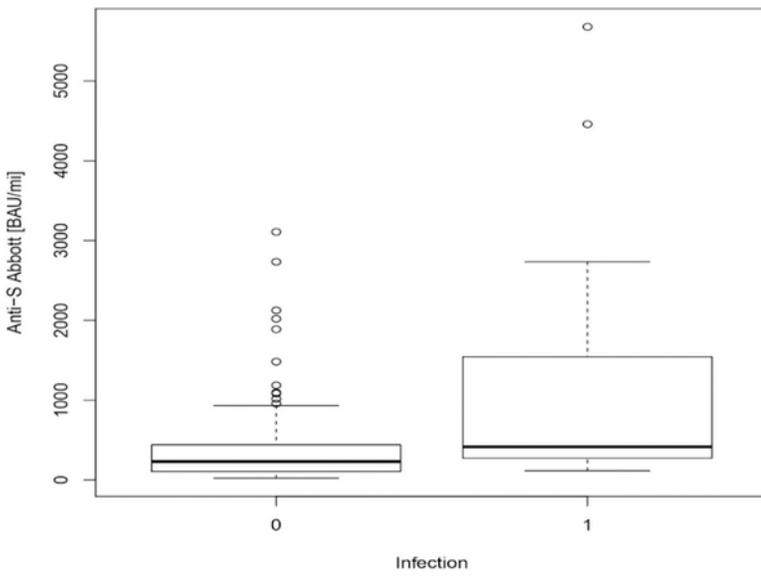


**Figure 1**

Teachers self-reporting systemic and local adverse effects after ChAdOx1 vaccination, n=192.



(A)



(B)

**Figure 2**

Antibody responses among 192 teachers following second vaccination with ChAdOx1 by prior infection.