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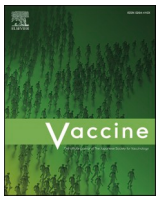

Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in children aged 6–17 years: Final results of a phase 2, single-blind, randomised controlled trial (COV006)

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ABSTRACT

Background: Paediatric COVID-19 vaccination programmes were initiated in response to the coronavirus pandemic declared by the World Health Organisation (WHO) in 2020. Ten COVID-19 vaccines received WHO Emergency Use Listing, however, only five were approved for use in children. ChAdOx1 nCoV-19 (AZD1222) was approved in adults in a two-dose regimen. We previously reported interim findings of a phase 2 study of ChAdOx1 nCoV-19 in children with immunogenicity, comparable with adults. Final results after 12 month follow-up are reported.

Methods: Single-blind, randomised controlled trial across four UK centres, recruiting 261 children and adolescents (aged 6-17 years). Participants received either two doses of ChAdOx1 nCoV-19 or Bexsero vaccine (controls). The primary outcome was safety (adverse events for 28 days following vaccination and serious adverse events throughout), and secondary outcome was immunogenicity (measured by SARS-CoV-2 anti-spike enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunosorbent spot (ELISpot)).

Findings: Five serious adverse events and four adverse events of special interest were reported. None were related to study vaccinations, and there were no deaths. Geometric mean titres (GMTs) from an anti-spike (Wuhan) ELISA in participants aged 6-11 years were 1 EU/ml (95% CI 1-2) at baseline versus 796 EU (95% CI 161-3948, n =4) at D364. In participants aged 12-17 years, GMTs were 1 EU/ml (95% CI 1-2, n=3) at baseline versus 1432 EU/ml (95% CI 2337-6083; n=6) at D364 (2 dose regimen at 112-day interval), compared to 3 EU/ml (95% CI 0-62) at baseline versus 392 EU/ml (95% CI 24, 6493; n=3) at D364 (2 dose regimen at a 28-day interval).

Interpretation: A two-dose regimen of ChAdOx1 nCoV-19 was immunogenic and safe in the trial population. No vaccine-related serious adverse events were reported. Immune responses persisted to 12 months in participants who did not experience breakthrough infection, This trial was registered with ISRCTN, trial number 15638344.

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1. Introduction

The burden of severe disease and death caused by the COVID-19 pandemic fell primarily on older populations and those with pre-existing comorbidities. As vaccines became available globally in 2021, health care workers and older adults were prioritised for COVID-19 vaccine roll out. The World Health Organisation (WHO) subsequently acknowledged that risk-benefit analyses supported the vaccination of all age groups to reduce infections, hospitalisations, deaths and long COVID. Several risk factors for severe COVID-19 disease in children have been identified, including obesity and certain pre-existing conditions [1]. While the benefits of vaccination of children at very low risk were debated [2], one justification was the emergence of a hyper-inflammatory syndrome temporally associated with SARS-CoV-2 infection in 2020 (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) in Europe, also known as multisystem inflammatory syndrome in children (MIS-C) in North America. Its incidence has decreased with subsequent waves of SARS-CoV-2 infection [3]. As vaccine supply became established in 2021, the WHO recommended that children with comorbidities or who were immunocompromised should be offered vaccination [4].

The WHO approved five vaccines for use in the children under the age of 18, whole inactivated virus vaccines BBIBP-CorV and CoronaVac, protein subunit vaccine NVX-CoV2373, and mRNA vaccines BNT162b2 and mRNA-1273.

Immunity generated by a priming series of BBIBP-CorV was shown to persist until 6–8 months post second-dose in children. Following two doses of CoronaVac, neutralising antibody titres measured 364 days after a second dose were approximately 1/6th of those measured 28 days after the second dose [5]. A single-centre follow-up study of patients 8–22 years of age with cancer receiving BNT1626b2 showed that seroconversion after two or three doses persisted beyond 12 months [6]. It is now established that heterologous boosting (i.e. the administration of a third dose of a different vaccine) can be more immunogenic than homologous boosting both in children and adults, emphasising the need for paediatric immunogenicity and vaccine efficacy data from a diverse range of vaccine platforms. However, there are limited data describing the efficacy of these vaccines in children under the age of 18 as formal phase III studies have not been published.

By contrast, ChAdOx1 nCoV-19 was a viral vectored vaccine approved by the WHO for use in adults over the age of 18 years. Some 3 billion doses of the ChAdOx1 nCoV-19 (AZD1222) were distributed globally, and it is estimated that in 2021 the vaccine saved approximately 6.3 million lives [7]. Real world data show the vaccine was highly effective and that the ancestral SARS-CoV-2 strain vaccine remained effective against emerging variants including Omicron [8]. Immunogenicity data from the Beta variant vaccine AZD2816 have been published showing neutralisation of that virus using an updated vector insert. ChAdOx1 nCoV-19 vaccine has also been used as a third-dose booster in campaigns in several countries including Brazil and Thailand [9]. ChAdOx1 nCOV-19 was withdrawn from the global marker in March 2024. AstraZeneca cited the main reason being a 'surplus of available updated vaccines' and consequently, a decline in demand for ChAdOx1 nCoV-19.

We previously reported preliminary safety and immunogenicity data from a phase II study of astandard two-dose schedule of ChAdOx1 nCoV-19 in children aged 6–17 years, covering a 182-day follow-up period. Whilst the vaccine no longer remains on the market, this was the first study where the viral vector had been given in a homologous regimen to children and therefore provided unique insights into its use as a vaccine. The vector remains under clinical development for other outbreak diseases [ref]. This is a report of the complete follow-up period for the phase 2 trial, including safety and immunogenicity data until 365 days post prime vaccination.

2. Methods

2.1. Study design and participants

Details of the study design, randomisation and masking approach, and procedures, including those affected by study amendments, have previously been published [10], covering the period from enrolment up to 28 days after a second dose of vaccine was received (D56 for participants receiving a second dose of vaccine at D28, and D140 for participants receiving a second dose of vaccine at D112). Participant characteristics were also previously reported.

Briefly, in February 2021 healthy volunteers 6–17 years of age were recruited in Oxford, London, Bristol and Southampton with exclusions made for chronic respiratory conditions and previous laboratory-confirmed COVID-19 infection. Computer-generated randomisation lists were used to randomly assign participants (4:1:4:1) in block sizes of 10 to receive two doses of intramuscular (right or left deltoid) ChAdOx1 nCoV-19 (batch number A03670) or capsular group B meningococcal vaccine with a 28-day or 84-day interval between doses. Members of the clinical team enrolled participants and assigned interventions following randomisation. Participants were blinded by concealing the appearance of the administered vaccine in a container.

During the recruitment period for the study, the Joint Committee on Vaccination and Immunisation advised the UK Government that individuals under 30 years of age who had not yet received the first dose of ChAdOx1 nCOV-19 vaccine should be offered an alternative vaccine. This was due to safety concerns regarding vaccine-induced thrombosis and thrombocytopenia [11]. At this point, 252 participants had been randomised and therefore recruitment was stopped at this point. Second-dose vaccination was briefly paused pending a review by the MHRA, who then authorised the administration of all remaining second doses in the study. However, this pause led to a delay in administration of vaccine, leading to all participants 12–17 years of age initially randomised to a 84-day interval receiving a second dose at day 112, and all participants 6–11 years of age receiving their second dose at day 112, as all of the younger group had yet to receive a second dose.

This report includes the trial period from 28 days after second dose of vaccine to the end of the study follow-up period (364 days after receiving the first dose of vaccine). During this time, safety reporting of serious adverse events (SAEs) and adverse events of special interest (AESIs) continued. Participants were unblinded upon request when they became eligible for the national SARS-CoV-2 vaccination scheme in the UK (16–17 years 23rd August 2021; 12–15 years 20th September 2021).

Participants continued to self-report positive SARS-CoV-2 episodes (defined as either a positive lateral flow or polymerase chain reaction (PCR) test in the community, with or without symptoms) and were asked to notify the study team if they received a COVID-19 vaccine in the UK national immunisation programme.

2.2. Outcomes

The primary objective of this study was to assess the tolerability of the vaccine in children aged 6–17 years, in a two-dose regimen with either a short or long dosing interval, which was previously reported. In this paper the results of secondary outcome measures for all timepoints up to D365 post first dose of vaccination, including humoral and cellular immunogenicity of ChAdOx1 nCoV-19, are reported.

2.3. Laboratory analysis

Pre- and post-vaccination humoral immune responses were measured via an in-house standardised total IgG ELISA against the ancestral trimeric SARS-CoV-2 spike protein and a SARS-CoV-2 pseudovirus neutralisation assay conducted as previously described. Anti-nucleocapsid IgG was measured at PPD laboratories by ECLIA. Cellular responses at baseline and 28 days after a first and second dose of vaccine

were measured by an in-house interferon-gamma ELISpot assay.

2.4. Statistical analysis

There was no formal hypothesis testing in this trial and immunogenicity analyses used samples from participants who were seronegative at enrolment (anti-nucleocapsid IgG negative at first vaccination). The results in this paper are primarily descriptive. Analyses were conducted on an intention-to-treat basis. Frequencies and percentages are presented for safety endpoints and geometric mean and 95 % confidence intervals (CIs) are reported for immunogenicity endpoints at D364. Time to event analysis was conducted using self-reported SARS-CoV-2 infection as the endpoint with censoring for receipt of an alternative COVID-19 vaccine in the national immunisation programme or withdrawal from the trial. Anti-nucleocapsid data was used to determine serological infection status at the end of the study. Participants were deemed seropositive if their anti-nucleocapsid titre had increased at least two-fold between 28 days post second vaccination and the final timepoint in the study,

We repeated an analysis of the data to adjust for the high infection rate and effect of the national paediatric COVID-19 immunisation programme in our cohort during the study. We censored the results of participants if they received an COVID-19 vaccine other than that administered in the trial, if they self-reported a SARS-CoV-2 infection or if their anti-nucleocapsid titre rose more than two-fold between 28 days after their second vaccination and the final D364 timepoint in the study. Participants who did not have an anti-nucleocapsid result at either 28 days post second dose or D364 were also excluded.

Survival analyses were conducted using R version 4.1.1 and descriptive statistics generated using GraphPad Prism version 10.

An independent data safety and monitoring committee provided safety oversight for this trial, ISRCTN registration number 15638344. The study protocol can be downloaded from the ISRCTN website.

2.5. Participant benefits

As previously outlined, all participants receiving the study vaccine ChAdOx1 nCoV-19 were offered a full 2-dose course of the active comparator capsular group B meningococcal vaccine at the end of the study.

2.6. Role of the funding source

This study was funded by AstraZeneca and NIHR who were not involved in the drafting of this article but approved a final version prior to publication.

3. Results

Study demographics for this trial have previously been published [10]. A consort diagram is shown in Fig. 1. The mean age was 8.7 years and 14.6 years in the 6–11 and 12–17 year groups, respectively. 49 % of participants were female. Of the 262 participants enrolled, 15 were seropositive at baseline of which 13 were randomised to receive ChAdOx1 nCoV-19. Four were enrolled in the younger cohort and 9 in the older cohort (of which four were in the 28-day interval group and five in the 112-day interval group). 230 participants completed the study period and contributed to the final analysis. The participants were recruited between February and April 2021 and the follow-up period was 12 months from date of enrolment.

3.1. Safety and reactogenicity

Details of the reactogenicity of ChAdOx1 nCoV-19, determined by solicited and unsolicited adverse event reporting in the 28 days following receipt of the first and second dose of the vaccine, have previously been published [10]. Five SAEs were reported (**Appendix 1**) within the 12-month follow-up period, of which four had been previously reported up to October 2021 and the final event occurring in January 2022. Three AESIs were recorded which have been previously reported. No SAEs or AESIs were deemed related to the study vaccinations. No suspected unexpected serious adverse reactions (SUSARs) or deaths were reported during the 12-month study follow-up period.

3.2. Immunogenicity

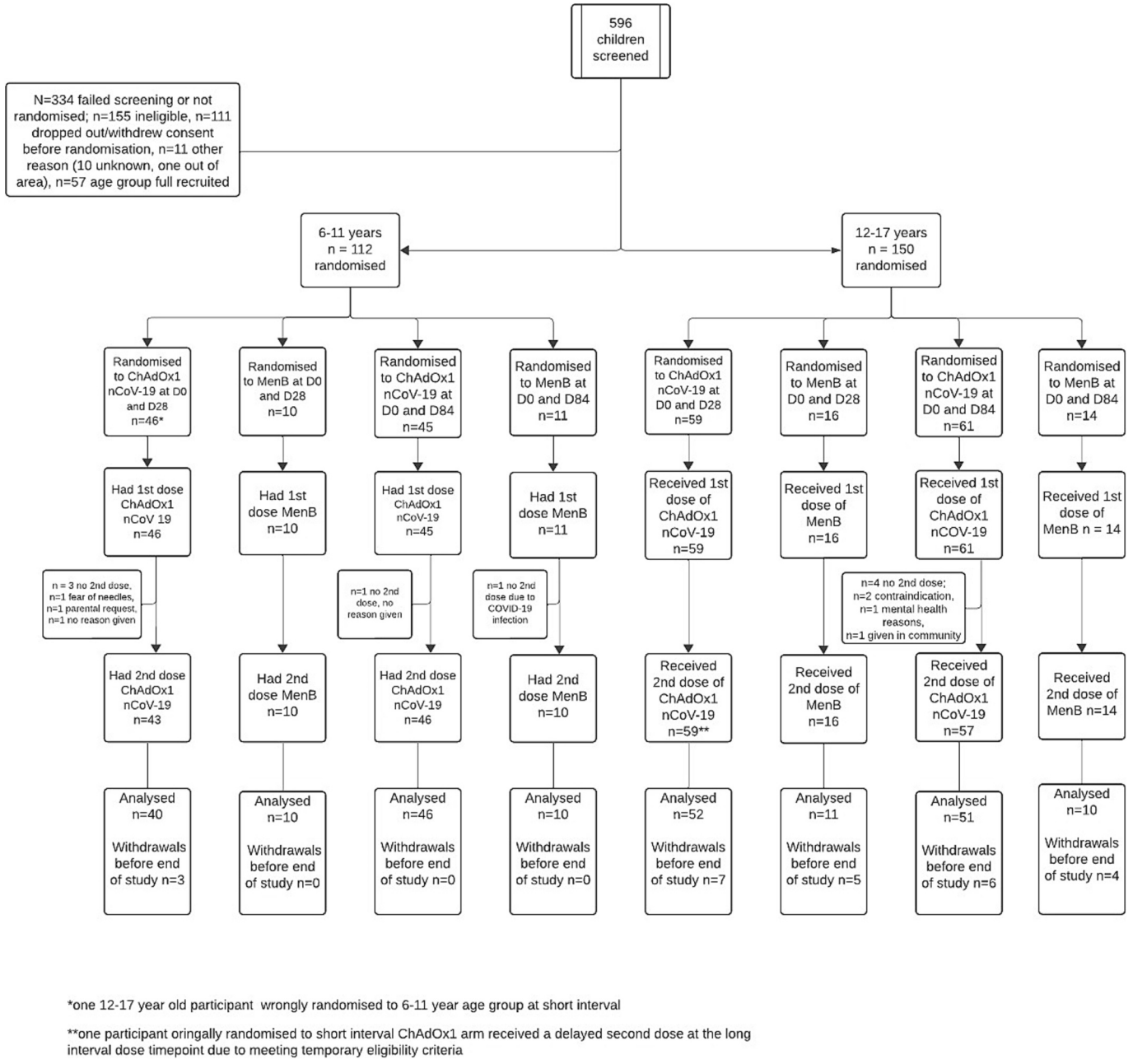
Among baseline seronegative participants, geometric mean titres (GMTs) of in-house ELISA anti-spike IgG at 364 days after a prime dose of ChAdOx1 nCoV-19 were highest in the older age group (Table 1; Fig. 2) who received a second dose at a 112-day interval (GMT 8265, 95 % CI 5291–12,911 EU/ml) compared with those who received a second dose at a 28-day interval (3738, 95 % CI 2172–6433 EU/ml) and those aged 6–11 years who received a second dose at a 112-day interval (3109, 95 % CI 2127–4544 EU/ml).

However, longitudinal immunogenicity data from ELISA, ELISpot and pseudovirus neutralisation assays (Tables 1 and 2) showed that measures of immunogenicity increased between 28 days after receiving a second dose of ChAdOx1 nCoV-19 (D56 or D140) and the final D364 post-prime timepoint, although a COVID-19 vaccine was not administered in the study during this period. Our cohort included children who self-reported SARS-CoV-2 infection or disclosed receiving a SARS-CoV-2 vaccination in addition to the vaccines given in this trial, when they became eligible for the UK paediatric SARS-CoV-2 vaccination programme in summer 2021.

A sensitivity analysis was performed to account for the high infection rate and effect of the national paediatric COVID-19 immunisation programme during the study. Higher anti-spike IgG titres than at baseline were seen across the ChAdOx1 nCoV-19 groups at day 364 ($n = 13$; Table 4). Among adolescents, anti-spike IgG titres were higher when there was a longer interval between the two priming doses (1432, 95 % CI 337–6083 EU/ml [$n = 6$] versus 392, 95 % CI 24–6493 EU/ml [$n = 3$]). Among the longer interval groups, titres were higher in older children than younger children (1432, 95 % CI 337–6083 EU/ml [n = 6] versus 796, 95 % CI 161–3948 [$n = 4$]).

Table 3 outlines self-reported SARS-CoV-2 infection episodes in trial participants. 110 cases of self-reported SARS-CoV-2 infection were reported to the trial team. 15 cases (14 symptomatic and 1 asymptomatic) were reported out of 52 participants in the control arm and 95 cases (72 symptomatic and 23 asymptomatic) were reported in 209 participants in the ChAdOx1 nCoV-19 arms. More cases were reported in the 12–17 age group who received two doses of ChAdOx1 nCoV-19 at a 28-day interval than at a 112-day interval (30 cases versus 23 cases).

There was no difference in the time to self-reported SARS-CoV-2 infections in the control and ChAdOx1 nCoV-19 arms (Fig. 3**)**. A similar number of breakthrough infections were reported in both age groups (53 in those aged 6–11 years, 57 in those aged 12–17 years). Despite a smaller number of participants in the younger age group the survival curves have similar gradients for both groups (Fig. 4). There was no difference (chi squared value 2.6; $p = 0.5$), in time to event for participants with a higher anti-spike total IgG antibody titre versus those with a lower anti-spike total IgG antibody titre at 28 days after receiving a second dose of vaccine (stratified by below/above median values). (See Fig. 4).



*one 12-17 year old participant wrongly randomised to 6-11 year age group at short interval

**one participant oringally randomised to short interval ChAdOx1 arm received a delayed second dose at the long interval dose timepoint due to meeting temporary eligibility criteria

Fig. 1. Flow chart of recruited participants for COV006.

Table 1
Data to accompany Fig. 2. Comparison of D364 anti-spike ELISA results in all participants who were seronegative at baseline. This includes participants who self-reported SARS-CoV-2 infection during the follow-up period of the trial. GM = geometric mean titre, V1 = day of first vaccination, V2 = day of second vaccination, EU = elisa units. Mean is followed by 95 % confidence intervals in parentheses, with the number of samples available at each timepoint listed after. MenB = Meningococcal Group B vaccine.

Groups		Anti-spike in-house ELISA GMT (95 % CI) [EU/ml]			
		V1	V2	V2 + 28 days	D364
6-11 years, 112-day interval	ChAdOx1 nCoV-19	1.5 (1–2), 77	405 (311–528), 69	2310 (1700–3138), 48	3109 (2127–4544), 54
	MenB	2 (1–4), 16	2 (1–4), 18	2 (1–2), 9	54 (8–379), 9
12–17 years, 112-day interval	ChAdOx1 nCoV-19	2 (1–2), 53	338 (243–470), 52	1963 (1575–2448), 45	8265 (5291–12,911), 45
	MenB	1 (1–1), 12	5 (1–17), 11	4.5 (1–17), 11	9321 (1296–67,041), 7
12–17 years, 28-day interval	ChAdOx1 nCoV-19	1.8 (1–2), 47	634 (497–810), 45	1194 (908–1568), 45	3738 (2172–6433), 38
	MenB	3 (1–5), 13	2 (1–5), 14	4 (2–10), 13	3293 (779–13,916), 9

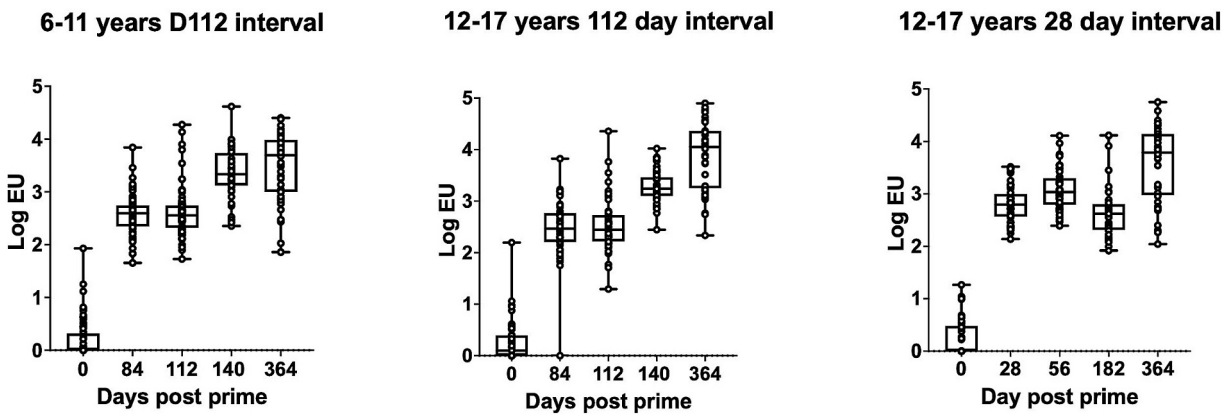


Fig. 2. Comparison of D364 anti-spike ELISA results in all participants who were seronegative at baseline. This includes participants who self-reported SARS-CoV-2 infection during the follow-up period of the trial.

4. Discussion

The data presented here show that the vaccine is safe and immunogenic in the trial population, across the age ranges and dosing intervals studied. Natural infection due to exposure to circulating SARS-CoV-2 in the UK and the availability of a UK paediatric COVID-19 vaccination programme was associated with increased anti-spike total IgG titres at the final 12-month timepoint across all COV006 trial age groups. After adjusting for infection defined by anti-nucleocapsid antibody titres and receipt of additional vaccine doses given out of the trial, we conclude that immunity against SARS-CoV-2 defined by anti-spike total IgG persists until at least 12 months following receipt of a second vaccine.

We previously showed that there is a significantly higher anti-spike IgG titre at 28 days following the second dose in the younger cohort (6–11 years) than the older cohort (12–17 years), who received two doses of ChAdOx1 nCoV-19 at an interval of 112 days. However, our findings at D364 suggest that further data would be needed to clarify whether waning of immunity is similar in older and younger paediatric groups. Although our data were insufficiently powered to formally model decay of total IgG levels, the results are consistent with analyses of adult ChAdOx1 nCoV-19 persistence data [12] which also suggest that waning of immunity follows a similar trajectory to other viral vectored vaccines such as Ad.26.CoV2·S [13], in contrast to mRNA vaccines which show a higher peak response after two doses but a sharper decline in antibody titre over six to eight months [14].

Although anti-nucleocapsid ELISA data were obtained for participants at all available sampling timepoints, the utility of these results was limited due to an unknown time lag between the participants being infected by SARS-CoV-2 and the study visit date. The date of the anti-nucleocapsid result could not be used as an accurate endpoint for time-to-event analysis. Our results may underrepresent the true burden of infection in our cohort as anti-nucleocapsid antibody responses are known to wane and infections in children are often asymptomatic [15].

Routine weekly nasopharyngeal swabbing was incorporated into the design of phase II/III adult ChAdOx1 nCoV-19 trials, together with additional blood testing when a participant tested positive for SARS-CoV-2. However, this approach was not used in COV006 due to the intention for it to be a phase II study only and concerns that additional blood tests would not be appropriate or acceptable in this age group.

The ChAdOx1 nCoV-19 vaccine used in this study was designed against the ancestral strain of SARS-CoV-2 which was first sequenced at the beginning of the pandemic. However, our trial participants were recruited in February–April 2021, and during the subsequent 12-month trial follow-up period are likely to have been exposed to Delta and Omicron variants which were circulating widely in the UK community at the time [8]. Real-word data has shown that protection against infection by emerging variants would be expected to be low, however the ancestral vaccine would still be expected to provide good protection against severe disease. Serum from individuals vaccinated with ancestral ChAdOx1 nCoV-19 has demonstrated reduced neutralisation against the Omicron lineage [16]. These findings are consistent with our observation that a similar number of breakthrough infections were observed in the treatment and control arms, and no cases of severe disease were observed in any of the trial groups.

ChAdOx1 nCoV-19 was immunogenic in our study cohort with immunogenicity persisting beyond 12 months. The size of this phase II study did not permit formal comparison of persistence of total IgG in adult and paediatric populations. Safety concerns have been raised about an association between the ChAdOx1 vector and vaccine-induced thrombocytopenia and thrombosis, and the mechanism underlying this association remains under investigation [17]. Whilst no safety concerns were raised within our cohort, the small size of this study limits our ability to detect most safety issues. Initial safety monitoring of ChAdOx1 nCoV-19 by AstraZeneca, based on over 49 million first doses administered to adults in the UK and EU, showed reporting rates of 8.1 cases of TTS per million vaccinees in the first 14 days after a first dose of the vaccine and 2.3 cases per million in the 14 days following a second dose of the vaccine [18]. Limitations in these data were acknowledged, including a reliance on healthcare-provider and vaccinee-reported data. Additional smaller, long-term follow-up safety studies of ChAdOx1 nCoV-19 have been published [19] but again may be limited in their ability to detect rarer events such as TTS.

Although ChAdOx1 nCoV-19 has now been withdrawn from the market, our data add to a limited number of published studies which describe the persistence of viral-vectored COVID-19 vaccine-induced immunity in children and support the use of viral-vectored COVID-19 vaccines in this age group.

Table 2
a and b. Comparison of D364 anti-spike ELISpot (2a) and pseudovirus neutralisation assay results (2b) in all participants who were seronegative at baseline. This includes participants who self-reported SARS-CoV-2 infection during the follow-up period of the trial.

a

		ELISpot in-house SFC per 10^6 PBMCs GM (95 % CI)			
		V1	V2	V2 + 28 days	D364
6-11 years, 112-day interval	ChAdOx1 nCoV-19	26 (22–31), 73	119 (90–158), 61	104 (79–137), 39	229 (171–305), 50
	MenB	21 (16–28), 18	22 (14–35), 13	19 (12−32), 6	66 (30–147), 8
12–17 years 112-day interval	ChAdOx1 nCoV-19	43 (33–55), 46	239 (187–306), 45	138 (97–195), 35	287 (195–421), 40
	MenB	43 (24–76), 11	64 (21–192), 11	30 (12–77), 8	226 (11–464), 6
12–17 years, 28-day interval	ChAdOx1 nCoV-19	33 (26–43), 43	295 (229–381), 45	256 (188–348), 42	217 (143–329), 40
	MenB	33 (20–54), 14	23 (15–34), 14	22 (15–32), 14	262 (86–800), 9

b

		PseudoNA (IC50, Mean)			
		V1	V2	V2 + 28 days	D364
6-11 years, 112-day interval	ChAdOx1 nCoV-19	1 (1–2), 80	258 (23–493), 68	2436 (767–4104), 49	1410 (1033–1788), 37
	MenB	–	–	–	2′5 (0–0), 1
12–17 years 112-day interval	ChAdOx1 nCoV-19	1 (1–4), 50	352 (134–839), 48	415 (306–524), 44	783 (−791–2357), 4
	MenB	0 (0–0), 12	10 (−12−33), 12	1064 (−1009–3137), 10	–
12–17 years, 28-day interval	ChAdOx1 nCoV-19	0 (0–0), 49	172 (−7–352), 46	247 (113–381), 47	1191 (710–1673), 17
	MenB	0 (0–0), 15	2 (−2, 6), 15	3250 (−39–104), 12	2819 (273–5364), 6

GM = geometric mean titre, V1 = day of first vaccination, V2 = day of second vaccination, SFC = spot forming cells, EU = elisa units, PBMCs = peripheral blood mononuclear cells, IC50 = 50 % inhibitory concentration. Mean is followed by 95 % confidence intervals in parentheses, with number of samples available at each timepoint listed after. MenB = Meningococcal Group B vaccine.

Table 3
Self-reported breakthrough infection episodes in COV006. Total number of episodes = 110. MenB = Meningococcal Group B vaccine.

Group	MenB arm (n = 51)			ChAdOx1 nCoV-19 arm (n = 211)		
	Total episodes	Symptomatic episodes	Asymptomatic episodes	Total episodes	Symptomatic episodes	Asymptomatic episodes
6–11 years, 112-day interval (n = 112)	**11**	11	0	**42**	33	9
12–17 years, 112-day interval (n = 75)	**0**	0	0	**23**	19	4
12–17 years, 28-day interval (n = 76)	**4**	3	1	**30**	20	10
Total	**15**	14	1	**95**	72	23

Table 4
Anti-spike antibody titres generated in response to two doses of ChAdOx1 nCoV-19. Vaccinations were given at V1 and V2 (28 or 112 days after V1). D364 denotes time elapsed since first dose at V1. EU = ELISA Units.

Groups	Anti-spike in-house ELISA (GMT, EU/ml)			
	V1	V2	V2 + 28 days	D364
6-11 years, 112-day interval	1 (1,1), 4	659 (48, 8985), 4	2794 (349, 22389), 4	796 (161, 3948), 4
12–17 years, 112-day interval	1 (1,2), 6	856 (108, 6789), 6	2488 (824, 7508), 6	1432 (337, 6083), 6
12–17 years, 28-day interval	3 (0,62), 3	1292 (156, 10703), 3	2506 (423, 14844), 3	392 (24, 6493), 3

Contributors

AJP and TL conceived and designed the trial and AJP is the chief investigator. AJP, TL, MDS, RS, GL, XL, AL and SR contributed to the protocol and design of the study. MRR, MDS, RS, PTH and SNF were the study site principal investigators. ALF, CD, EAC, FC and TL were responsible for laboratory testing and assay development. GL, XLand NGM accessed and verified the data, and did the statistical analysis. AJP, TL, NGM, XL, FC and GL contributed to the preparation of the report. HR, GL, PKA, RA, DS, KT and NS contributed to the implementation of the study. All other authors contributed to the implementation of the study and data collection. All authors critically reviewed and approved the final version.

Data sharing

Data can be made available upon reasonable request.

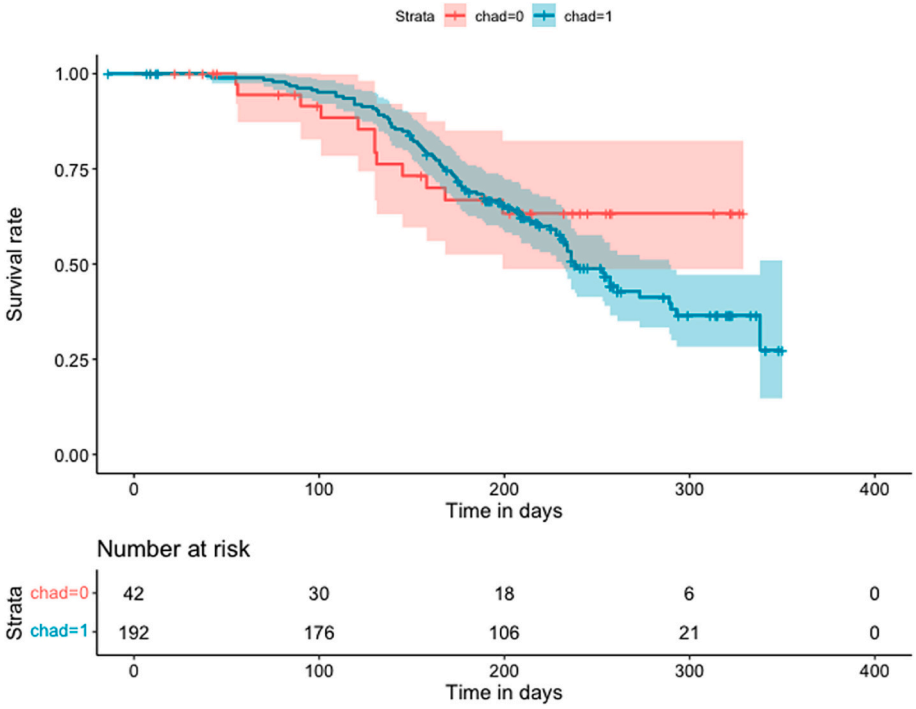


Fig. 3a. Survival curves comparing time to event (self-reported SARS-CoV-2 infection) in control group (chad = 0) with ChAdOx1 nCoV-19 recipient group (chad = 1). All COV006 participants who received 2 doses at 112-day interval were included in this analysis.

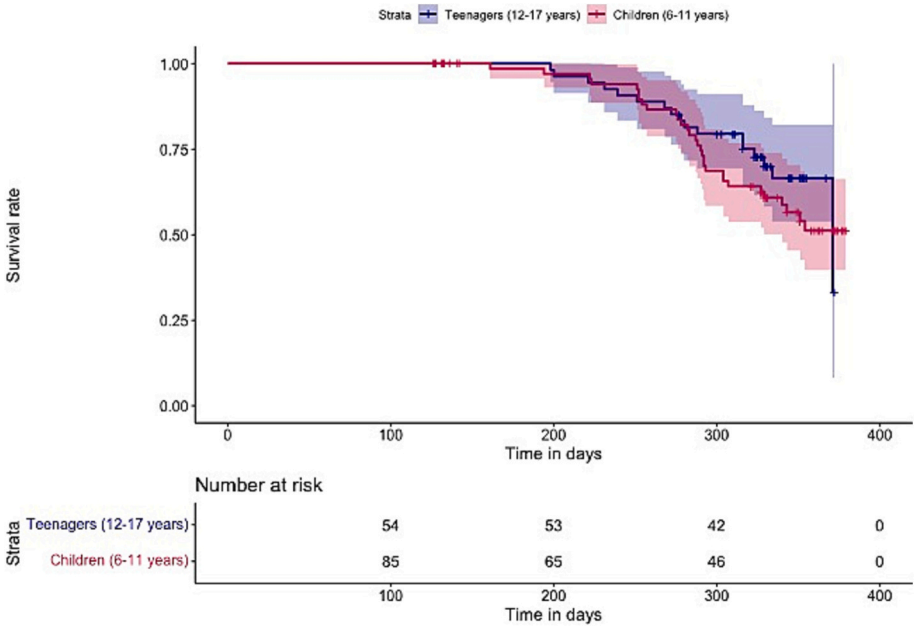


Fig. 3b. Survival curves comparing time to event (self-reported positive SARS-CoV-2 lateral flow or PCR result) in COV006 participants who received two doses of ChAdOx1 nCoV-19, 112 days apart. Censoring reflects participants who withdrew from the study or who received an alternative COVID-19 vaccine in the UK national immunisation programme. Follow-up time starts 14 days after the second vaccine dose was received.

CRediT authorship contribution statement

Grace Li: Formal analysis, Writing – original draft, Writing – review & editing. **Natalie G. Marchevsky:** Writing – review & editing. **Grace Macaulay:** Writing – original draft, Writing – review & editing. **Parvinder Aley:** Project administration, Writing – review & editing. **Hannah Baughan:** Project administration, Writing – review & editing. **Emma Plested:** Project administration. **Sagida Bibi:** Data curation, Project administration, Supervision, Writing – review & editing. **Federica Cappuccini:** Data curation. **Saul N. Faust:** Supervision, Writing – review & editing. **Paul T. Heath:** Supervision, Writing – review & editing. **Jill Muller:** Project administration, Writing – review & editing. **Hannah Robinson:** Project administration, Writing – review & editing. **Marion Roderick:** Supervision, Writing – review & editing. **Matthew**

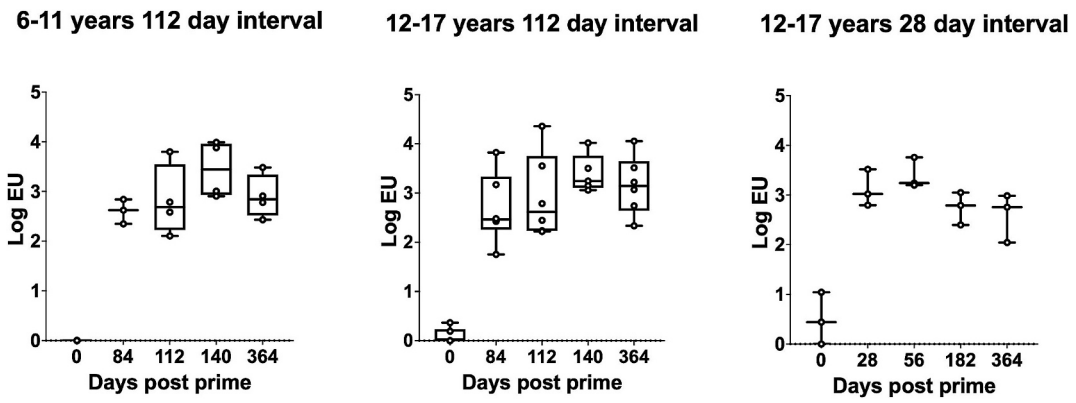


Fig. 4. ChAdOx1 nCoV-19 recipients only. EU = Elisa Units.

Snape: Supervision. **David Smith:** Project administration, Supervision. **Rinn Song:** Supervision. **Xinxue Liu:** Methodology, Supervision, Writing – review & editing. **Teresa Lambe:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Andrew J. Pollard:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AJ Pollard as director of Oxford Vaccine Group reports financial support was provided by AstraZeneca Pharmaceuticals LP. AJP is chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation but did not participate in policy advice on coronavirus vaccines during the pandemic. He was a member of the WHO Strategic Advisory Group of Experts (SAGE) until 2022. AJP is chief investigator on clinical trials of Oxford University's COVID-19 vaccine funded by NIHR. TL is named as an inventor on a patent application covering the ChAd vaccine and is an occasional consultant to Vaccitech, unrelated to this work. Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19 and AJP, TL, SB, GL are contributors under the licence agreement. MDS acts on behalf of the University of Oxford as an investigator on studies funded or sponsored by vaccine manufacturers, including AstraZeneca, GlaxoSmithKline, Pfizer, Novavax, Janssen, Medimmune, and MCM. He receives no personal financial payment for this work. SNF acts on behalf of University Hospital Southampton NHS Foundation Trust as an investigator or provides consultative advice on clinical trials and studies of COVID-19 and other vaccines funded or sponsored by vaccine manufacturers, including Janssen, Pfizer, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Sanofi, Medimmune, Merck, and Valneva. He receives no personal financial payment for this work. PTH acts on behalf of St George's University of London as an investigator on clinical trials of COVID-19 vaccines funded or sponsored by vaccine manufacturers, including Janssen, Pfizer, AstraZeneca, Novavax, Moderna and Valneva. He receives no personal financial payment for this work. All other authors declare no competing interests. AstraZeneca reviewed the final manuscript before submission, but the authors retained editorial control. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127597.

Data availability

Data will be made available on request.

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