

Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil; an exploratory analysis of a randomised controlled trial

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Abstract

Background Emerging evidence shows the substantial real-world impact of authorised vaccines against COVID-19 and provides insight into the potential role of vaccines in curbing the pandemic. However, there remains uncertainty about the efficacy of vaccines against different variants of the virus. Here we assessed efficacy of ChAdOx1 nCoV-19 (AZD1222) against lineages of SARS-CoV-2 circulating in Brazil from June 2020 until early 2021.

Methods Participants aged 18 and above were enrolled into a randomised phase 3 trial of ChAdOx1 nCoV-19 vaccine against symptomatic SARS-CoV-2 infection. Participants received two doses of ChAdOx1 nCoV-19 or control (1st dose: Men ACWY vaccine, 2nd dose: normal saline). Nasopharyngeal and oropharyngeal swabbing was performed if participants developed symptoms of COVID-19 (cough, shortness of breath, fever >37.8°C, ageusia, anosmia). Swabs were tested by nucleic acid amplification (NAAT) for SARS-CoV-2, sequenced, and viral load determined. For those samples where a genotype could not be ascertained from sequencing, allele specific PCR was performed. The efficacy analysis included symptomatic COVID-19 in seronegative participants with a NAAT positive swab more than 14 days after a second dose of vaccine. Participants were unblinded after the vaccine was authorised for use, and the control participants offered vaccination. Infections occurring after unblinding were excluded from analysis. Vaccine efficacy was calculated as $100\% \times (1 - \text{relative risk (RR)})$, where RR was estimated from a robust Poisson model. The trial is registered at ISRCTN89951424.

Findings 9433 participants were eligible for inclusion in the pre-specified primary efficacy population, having reached more than 14 days after a second dose of ChAdOx1 nCoV-19, of whom 307 were NAAT+, in this post-hoc analysis. From June 2020 to February 2021, the two most frequently identified lineages were P.2 (N=153) and B.1.1.28 (N=49). P.1 emerged during the study (N=18) but became dominant only after study unblinding. Viral loads were highest amongst those with P.1 infection. Vaccine efficacy (VE) for B.1.1.33 (88.2%, 95%CI 5, 99), B.1.1.28 (73%, 95% CI, 46, 86), P.2 (69% 95% CI, 55, 78) and P.1 (64%, 95% CI, -2, 87) was estimated. In participants who had received two doses of vaccine, one COVID-19 hospitalisation occurred in the ChAdOx1 nCoV-19 group and 18 in the control group, with VE against hospitalisation 95% (95% CI 61, 99). There were 2 COVID-19 deaths in the control group and none in the vaccine group.

Interpretation ChAdOx1 nCoV-19 provides high efficacy against hospitalisation, severe disease and death from COVID-19 in Brazil and there is strong evidence of protection being maintained against P.2, despite the presence of the spike protein mutation E484K. Real world effectiveness studies are ongoing in Brazil to further establish protection against P.1 and other emerging variants.

Research In Context

Evidence before this study

On 25th May 2021 we searched Medline for the search terms regarding SARS-CoV-2, vaccination and variants of concern or Brazil (full search strategy in supplementary materials Box S1) and returned 504 articles. Search of the preprint MedRxiv server showed 15,230 results when “B.1*” was included as a search term due to a large number of papers on the B.1.1.7 and B.1.351 variants of concern, narrowing to 572 when P.1 and P.2 alone were used as search terms. P.1 infections have been shown to have higher viral loads, and there is accumulating in vitro evidence of reduced efficacy of existing vaccines, including mRNA1273, BNT162b2, ChAdOx1 nCoV-19, and CoronaVac.

Four articles evaluated efficacy or effectiveness of a SARS-CoV-2 vaccine in Brazil. Evidence from a trial of inactivated vaccine (CoronaVac)¹ and an adenoviral vectored vaccine (Ad26.CoV2.S) showed good efficacy against moderate-severe COVID-19². The efficacy of CoronaVac was reduced for any symptomatic COVID-19 infection compared with moderate to severe infection¹. The primary analysis for ChAdOx1 nCoV-19 vaccine which included data from Brazil, the UK, and South Africa showed good efficacy against symptomatic COVID-19. These studies were performed prior to P.1 becoming the dominant lineage. A test negative case control effectiveness study of older adults in São Paulo State estimated a further reduction in efficacy for CoronaVac against any symptomatic COVID-19 disease at a time when P.1 was established.³

Added value of this study

This study demonstrates efficacy of the ChAdOx1 nCoV-19 vaccine against lineages B.1.1.33, B.1.1.28 and P.2 and against severe disease in a randomised controlled trial, and provides preliminary data on efficacy against P.1.

Implications of all the available evidence

Multiple SARS-CoV-2 variants of concern show in vitro evidence of immune evasion. There is growing evidence that vaccine efficacy and effectiveness against mild-moderate disease may be compromised by variants of concern. However, other non-neutralising binding antibodies and T cells may confer protection against severe disease in the absence of strong neutralising antibody. Adequate genomic surveillance especially in areas of high transmission is essential. Booster vaccinations may be required, the timing, nature, and number of which remains to be established.

Introduction

The SARS-CoV-2 pandemic continues to cause global impact. Spike protein-based SARS-CoV-2 vaccines have shown effectiveness in several countries^{4,5} enabling the relaxation of non-pharmaceutical interventions in some settings. The emergence of SARS-CoV-2 variants prompts questions about the ongoing protection elicited by existing vaccines. The risk of vaccine escape, whereby vaccine generated immunity is insufficient to provide protection against disease, is a concern. High virus transmission in combination with the presence of convalescent or vaccine-mediated immunity may drive selection of escape mutants. These theoretical concerns are broadly supported by in vitro data showing reduction in neutralising antibody titres, but efficacy or clinical effectiveness of existing spike-based vaccines against the B.1.1.7 variant of concern (VOC) does not seem to be compromised.^{6,7} However such vaccines have

a reduced efficacy against the B.1.351 VOC that possesses additional spike mutations⁸⁻¹⁰ and may translate into reduced vaccine effectiveness.¹¹ Nevertheless, several lines of evidence indicate that efficacy against severe disease may be preserved against current identified VOCs.

Brazil has experienced more than 16 million confirmed cases and over 450 000 deaths to date,¹² with the Amazon region being particularly severely affected.¹³ Lineages B.1.1.33 and B.1.1.28 were dominant throughout Brazil during 2020.¹⁴ Towards the end of 2020, two sublineages of B.1.1.28, designated P.2 and P.1, emerged and spread rapidly through the population.^{14,15} Prior infection with earlier lineages may not confer adequate or sustained protection in the face of emerging variants¹⁶. For example, areas in Brazil with suspected high seroprevalence rates have seen subsequent exponential growth of infections.¹³ This contrasts with the protection from reinfection for a median of 7 months duration seen in a large healthcare worker (HCW) study in the UK during a period when B.1 lineages were circulating and the B.1.1.7 variant arose.¹⁷ Symptomatic reinfections in immunocompetent adults with P.1 and P.2 sublineages have been described (following B.1 and B.1.133 infections respectively).^{18,19}

Both the P.1 and P.2 sublineages harbour the E484K mutation in the receptor binding domain (RBD) of the spike protein. E484K has been associated with *in vitro* immune escape from therapeutic monoclonal antibodies,²⁰⁻²² prompting the withdrawal of the emergency use authorisation for bamlanivumab in the US.²³ The E484K mutation is observed to have arisen independently in other variants such as B.1.351²⁴ and features as an additional mutation in recent samples of established VOCs such as B.1.1.7²⁵. Whilst P.2 harbours no other lineage-specific spike mutations, P.1 has additional RBD mutations, most notably K417T and N501Y. The coincident emergence of N501Y, K417T/N and E484K mutations in P.1 and B.1.351^{24,26} is suggestive of convergent evolution.^{15 27,28-30}

The shared triplet of RBD mutations might suggest that the pattern of *in vitro* responses^{31,32} and reduced efficacy of ChAdOx1 nCoV-19⁸ for B.1.351 may be echoed for P.1. However, early *in vitro* data showed two monoclonal antibodies retained activity against P.1 whilst showing no neutralization against B.1.351.^{22,31} Convalescent sera from individuals infected early in the pandemic and from mRNA and viral-vectored vaccine recipients showed a reduction in P.1 neutralization activity for both pseudovirus and live coronavirus²² but not to the extent seen for B.1.351.³³ Early data for an inactivated vaccine in Brazil when P.1 was dominant also suggest there may be a reduction in effectiveness.³

In this paper we report the findings from a multisite Brazilian COVID-19 vaccine efficacy study assessing the efficacy of the ChAdOx1 nCoV-19 vaccine in preventing symptomatic COVID-19 disease caused by the individual circulating SARS-CoV-2 lineages.

Methods

Overview. An ongoing randomised controlled phase 3 multi-site trial of the efficacy of the ChAdOx1 nCoV-19 vaccine was conducted in Brazil that began on June 23, 2020. Efficacy and safety data as well as the full study protocol have been previously published.^{34,35}

Study design and participants. This multi-centre study assessing the safety and efficacy of ChAdOx1 nCoV-19 vaccine was performed at six sites across Brazil (São Paulo, Rio de Janeiro, Salvador, Natal, Santa Maria, Porto Alegre) (supplementary figure 3). Individuals aged 18 and over at high risk of exposure to SARS-CoV-2, with healthcare workers prioritised for enrolment.

Participants were screened for inclusion and exclusion criteria, underwent medical history review, clinical observations and history-directed clinical examination.

Participants were randomised to receive either ChAdOx1 nCoV-19 ($3.5-6.5 \times 10^{10}$ viral particles) or MenACWY conjugate vaccine as a control, administered as an intramuscular injection. Participants randomised to the control group received saline as their second dose. In response to emerging data from our phase 1 ChAdOx1 nCoV-19 study showing a rise in neutralising antibody with a second dose,³⁶ all participants were offered a second dose with a dose interval of between 4 and 12 weeks (median 35 days, IQR 32, 47). Participants, clinical investigators and laboratory staff were blinded to vaccine allocation. Following emergency use authorisation of ChAdOx1 nCoV-19 and an inactivated SARS-CoV-2 viral vaccine in Brazil on 17th January 2021, all trial participants were unblinded to vaccine allocation. Participants in the control group were offered 2 doses of ChAdOx1 nCoV-19 within the trial with a dose interval in line with the national programme or could choose to accept the inactivated viral vaccine as part of the Brazilian national immunisation programme.

Participants were asked to contact their study site if they developed any one of: fever of $\geq 37.8^{\circ}\text{C}$, cough, shortness of breath or anosmia/ageusia. They were reminded weekly to do so throughout the trial. Symptomatic participants were invited for nasopharyngeal and oropharyngeal swabbing and a SARS-CoV-2 nucleic acid amplification test (NAAT) at their local clinical site. Samples were processed using commercial NAAT assays at local diagnostic laboratories listed in supplementary Table S5. Swabs were shipped to Oxford for sequencing and genotyping as described in the supplementary methods section.

Outcomes

The primary objective of the trial was to evaluate efficacy of the ChAdOx1 nCoV-19 vaccine against NAAT-confirmed COVID-19. The primary outcome was virologically-confirmed, symptomatic COVID-19, defined as a NAAT-positive swab combined with at least one of: fever $\geq 37.8^{\circ}\text{C}$, cough, shortness of breath, anosmia or ageusia. All NAAT positive cases occurring before participant unblinding were reviewed by a blinded independent endpoint adjudication committee who assigned severity scores using the WHO clinical progression score.³⁷ Only cases adjudicated by the committee as primary outcome cases were included in the analysis. Cases which occurred after unblinding and were not eligible for inclusion in efficacy analyses were adjudicated by an internal adjudication committee.

Analysis by lineage is a post-hoc exploratory analysis.

Statistical Methods

Participants were included in primary efficacy analyses if they were seronegative to the nucleocapsid protein at baseline, received two doses of vaccine, had follow up for at least 15 days after the second dose, and no prior evidence of infection. Cases were included in the efficacy analysis if a lineage was obtained from processing the swab taken for diagnosis, COVID-19 symptoms occurred on day 15 after the second dose or later, and before the participant was unblinded as to the vaccines they had received. In addition, some participants received a COVID-19 vaccine outside of the trial and were censored in the analysis at this time point.

Symptomatic cases occurring more than 21 days after a first dose but before the 15 day post-second dose timepoint were considered secondary endpoints for efficacy analyses.

Vaccine efficacy was defined as $100\% \times (1 - \text{relative risk (RR)})$, where RR was estimated from a robust Poisson model using SAS "*proc genmod*". The log of the number of days of follow up was included as an offset in the model.

To determine if the SARS-CoV-2 lineage affected the viral load for the case, viral load data was compared across variants for swabs from cases included in the efficacy analysis, and separately from all processed swabs combined regardless of vaccines received. Viral loads were compared using the Kruskal-Wallis test.

Swabs were not available from all cases as some participants accessed NAAT tests at non-study sites and at one site a freezer malfunctioned. A sensitivity analysis was conducted using multiple imputations to impute the missing lineage data from unavailable swabs under a missing at random assumption. The imputation model generated a value from a three-component multinomial (categorical) variable in which the three components corresponded to 'P1 variant', 'P2 variant' or 'other variants'. The probabilities used to generate the imputed value were obtained from the site-specific distribution of P1 to P2 to other variants on the week the case occurred. The allowed for the chronological and geographical spread of new variants to be incorporated into the imputation. 100 imputation datasets were generated and the log-RR and its standard error stored for each iteration. The 100 imputed log-RRs were combined using Rubin's rules^{38,39} in SAS "*proc mianalyze*".

The data cut-off date for this analysis was February 28, 2021 at which point the majority of participants in the trial were unblinded and further accrual of cases for efficacy analyses were no longer possible. Cases occurring after this date were not included in the analysis.

The trial is registered at ISRCTN89951424.

Role of the funding source

UKRI, NIHR, Wellcome Trust, CEPI, Lemann Foundation, Rede D'Or, and Brava and Telles Foundation, NIHR Oxford Biomedical Research Centre, and AstraZeneca.

AstraZeneca reviewed the final manuscript before submission, but the academic authors retained editorial control. All other funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

There were 10416 participants enrolled and randomised into the study between June 23, 2020 and December 1, 2020. 9433 participants received two doses and met the criteria for inclusion in this analysis. Reasons for exclusion are shown in Figure 1.

677 clinical samples were shipped and processed. Of these, 307 (45%) came from cases of primary symptomatic COVID-19 meeting the definition for inclusion in the efficacy analysis, and 236 (77%) of these primary cases had sufficient intact specimen for lineage assignment through sequencing or genotyping. Some participants had more than one positive swab for the same event.

Demographics

Demographic and baseline characteristics of the primary efficacy cohort were well balanced (Table 1). 82% of the participants were aged 18-55 years and 70% identified as white. 65% worked in a health or social care setting.

Lineages

The most prevalent lineage identified was P2 in 153 cases, followed by the ancestral B.1.1.28 lineage in 49 cases. Unblinding of study participants began at a similar time as the appearance of the P1 variant and only 18 cases were able to be included in the analysis (Figure 2A, B).

Vaccine efficacy was similar for the all variants. Efficacy for B.1.1.28 was 73%, (95% CI, 46, 86), and for P2 was 69% (95% CI, 55, 78). Fewer cases were available for analysis of efficacy for B.1.1.33 (VE 88.2%, 95%CI 5, 99), and P1 (64%, 95% CI, -2, 87) which had wide confidence intervals. Efficacy was not computed for cases of N.9 (N=4), N.6 (N=1) or B.1.1.7 (N=1) as there were fewer than 5 instances of each. Multiple imputation of missing swabs gave similar estimates for P1 and P2 lineages as the complete case analysis (Table 2).

Primary outcome hospitalisation cases, occurring more than two weeks after a second dose, were present in 1 and 18 participants in the ChAdOx1 nCoV-19 and control groups respectively, VE 95% (95% CI 61, 99). The one hospitalised participant in the ChAdOx1 nCoV-19 group had a WHO score of 5, but no swab was available for processing to determine lineage. There were no severe cases nor deaths in the vaccinated arm. Among the participants meeting the criteria

for primary efficacy analysis, there was one death due to COVID-19 in the control arm, and 6 further cases were classified as severe COVID-19 (WHO score \geq 6), giving 100% efficacy (95% CI 34, NE) against severe COVID-19 with two doses of vaccine (Table 3, Supp Table 1). A second death occurred in the control arm more than 21 days after the first dose of vaccine but before the second dose was received.

Viral load varied by SARS-CoV-2 lineage ($p=0.0002$) with the P.1 lineage having the highest median viral load (Figure 3, Table S2).

Discussion

In this post-hoc exploratory analysis, ChAdOx1 nCoV-19 provided protection against severe disease and death in Brazil, the key endpoints to protect lives and safeguard medical infrastructure from being overwhelmed. This analysis also shows vaccine efficacy against the dominant lineages causing symptomatic COVID-19 infection in our participants: P.2 and B.1.1.28. There were relatively few cases of the B.1.1.33 and P.1 lineages observed in the timeframe prior to unblinding, and assessment of efficacy for these variants was underpowered. The distribution of P.1 cases observed suggest that protection against symptomatic disease for this variant may be maintained but slightly reduced in comparison with P.2 or the parent lineage B.1.1.28. However, the limited number of cases available for analysis makes it difficult to draw firm conclusions. There were a greater number of P.2 cases, for which ChAdOx1 nCoV-19 showed similar efficacy compared with the parent B.1.1.28 lineage.

All first-generation spike-based COVID-19 vaccines that are currently in clinical use were generated from the ancestral Wu-1 spike gene sequence, raising the potential for loss of vaccine efficacy as SARS-CoV-2 accumulates mutations during viral evolution. The phase 3 multi-site study of an inactivated virus vaccine, (CoronaVac) conducted in Brazil between July and December 2020 showed a secondary endpoint of efficacy against moderate-severe disease of 100% (95% CI, 56.4 to 100.0).¹ However, the primary endpoint of vaccine efficacy against any symptomatic disease was 50.7% (95% CI 35.9 to 62.0). A subsequent test-negative case control study of the inactivated vaccine evaluated the same endpoint amongst older adults during periods of P.1 dominance.³ This study estimated a two dose vaccine effectiveness of 36.8% (95% CI -54.9 to 74.2) but these figures are difficult to compare due to the different study types and participant demographics, as well as different prevailing lineages and very limited sequencing during the two study periods. Our observations of vaccine efficacy of ChAdOx1 nCoV-19 against symptomatic disease in this report are consistent with our primary combined analysis of efficacy from studies in Brazil, the UK, and South Africa, in which VE was 66.7% (57.4 to 74.0). The single-dose adenovirus vectored vaccine (Ad26.COV2.S) phase 3 data. This vaccine showed efficacy against moderate to severe-critical COVID-19 disease of 68.1% (95% CI, 48.8 to 80.7) where P.2 formed the majority of the sequences obtained.²

Our data are also in keeping with the high levels of protection against severe disease caused by other variants such as B.1.351 by BNT162b2 and NVX-CoV2373.^{40,41} However, the positive findings from this study for P.2 are in contrast to the lack of observed efficacy seen for ChAdOx1 nCoV-19 against mild-moderate disease caused by B.1.351.⁴² There is a wide clinical spectrum of SARS-CoV-2 infection, from asymptomatic to severe COVID-19 disease requiring multi-organ support. The immune responses required to protect from asymptomatic disease may differ in nature or magnitude from those required to protect against severe disease which may in turn have implications for the ability of SARS-CoV-2 vaccines to reduce transmission. Animal data from the ChAdOx1 nCoV-19 vaccinated hamster model showed a reduction in virus neutralising antibody titre with B.1.351 compared with B.1.1.7. However when challenged with either of these lineages, the vaccinated animals did not have infectious virus or gross pathology in their lungs yet virus detectable in the upper respiratory tract of both vaccinated and control animals.⁴³

Ongoing antigenic drift of the SARS-CoV-2 virus due to error-prone RNA replication is inevitable and it is possible that vaccines will drive the selection of variants towards escape from neutralising antibodies and to increased transmissibility. Many of the RBD mutations that have arisen appear to be associated with immune evasion, transmissibility or both. The only RBD lineage defining mutation for P.2 lineage is the E484K mutation, whilst P.1 and B.1.351 harbour multiple RBD mutations. E484K (and a similar mutation E484Q) are being rapidly accumulated by lineages across distinct epidemiological and geographic settings and the addition of E484K/Q mutations to existing VOCs (such as B.1.1.7) is associated with evasion of neutralising antibodies.^{20,44} The observation that vaccine efficacy in our trial was preserved for P.2 may indicate that E484K, when occurring as an isolated RBD mutation, may be responsible for minimal reduction in protection. However, it is not known what the relative contribution of E484K/Q mutations may have on vaccine efficacy when occurring as part of a constellation of RBD mutations. A cautious approach to variants containing E484K and other RBD mutations is warranted whilst our understanding of their individual impact improves.

The viral load was highest in the P.1 cases consistent with other analyses.^{15,45} Higher viral loads may result in more shedding of virus, contributing to the greater transmissibility seen with this variant.¹⁵ It has been suggested that the time between onset of illness and NAAT testing might vary during the progression of the pandemic, confounding attempts to compare viral loads for different variants.⁴⁶ In our study there was a consistent median 4-day difference between illness onset and the collection date of the swab across all identified lineages thus comparisons of viral load are not confounded by this potential source of bias. Of note, samples with undetermined lineages had a larger median 8-day interval (IQR 6, 12) between illness onset and NAAT swab which may have resulted in the sample being taken at a time of reduced viral load making it more difficult to assign a lineage to the event.

The limitations of these data are that the sample size was determined by the number of samples from which a sequence sufficient to define lineage could be generated and was not sufficient to enable comparisons of efficacy between lineages. The evolution of the virus over time and between geographically distant trial sites resulted in a dataset with limited numbers in some lineage groups for efficacy analysis. Our study sites were situated in the South and East of Brazil which may explain the relatively small proportion of P.1 cases by the time of data cut-off. Phylogenetic evidence suggests this lineage arose in north west Brazil and a corresponding delay in observations from other parts of the country would be expected in line with epidemic spread.¹⁵ In addition, the trial participants were unblinded as to allocation arm to allow participants to be vaccinated once efficacy was established, as requested by the ethics committee, thereby necessarily truncating the participants' ongoing inclusion for efficacy analysis. The unblinding of the study occurred at a time when P.1 infections

were growing rapidly in our study site areas. There were 18 cases of P.1 included in the efficacy analysis and 160 that occurred after unblinding which could not be included in the efficacy analyses (supplementary table S2). However, every effort was made to assign a lineage for relevant samples obtained prior to unblinding by using a novel allele specific PCR method and missing data were imputed in a sensitivity analysis which yielded similar efficacy estimates to the complete case analysis. Our trial participants were also predominantly younger (<56 years) with relatively few co-morbidities, however despite this there was still evidence of protection against severe disease and death.

National roll-out of 2 COVID-19 vaccines, the Sinovac Biotech Ltd and Oxford/AstraZeneca vaccines, began in Brazil in January 2021, prior to study unblinding, and further vaccines have been subsequently approved for use. More than 20.1% of the population (total population ~212 million) had received at least one dose of a COVID-19 vaccine by 25th May 2021. Vaccine effectiveness studies are underway to evaluate real world impact on the pandemic in Brazil as vaccine trial efficacy of first-generation vaccines in most settings will no longer be attainable due to population vaccine roll out.

For next generation vaccines, studies to ascertain efficacy are likely to be based upon immunogenicity data showing equivalence to an as yet undefined immune correlate for protection which will be established from phase 3 trials. However, the variability of vaccine efficacy may be underpinned by genetic mismatch between the vaccine lineage and currently circulating virus.⁴⁷ Defining the correct immune correlate is challenging in the face of continued antigenic drift, and selection pressure from previous infection and vaccine induced immunity. Work is ongoing to establish the role of variant vaccines, heterologous schedules and booster regimes.

The likelihood that vaccine effectiveness may vary against emerging SARS-CoV-2 variants emphasises the need for the infrastructure for ongoing viral genomic surveillance. This is particularly important in countries where both viral transmission is high and vaccination coverage is limited, and may need support from international agencies.

Declarations

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Contributors

AJP and SCG conceived the trials and AJP is the chief investigator. AJP, SACC, LYW, DJ, KRWE, MNR, MV, PMF, TG contributed to the protocol and design of the study. SACC, LYW, AVDAM, EPM, AP, AVS, ES are study site principal investigators. PKA, EP, DJ, PMF, SB, MF, SK, YFM, contributed to the implementation of the study or data collection. NGM, and MV did the statistical analysis. TG, DB, JR, PS, conducted the sequencing and genotyping. AJP, TG, KRWE, MNR and MV contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Declaration of interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. SCG is cofounder of Vaccitech (collaborators in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) and a patent application covering this SARS-CoV-2 vaccine. PMF is a consultant to Vaccitech. AJP is Chair of the UK Department of Health and Social Care's JCVI, but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts (SAGE). AJP is a NIHR Senior Investigators.

Data sharing

Anonymised participant data will be made available when the trial is complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

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Tables

Table 1 Demographics and baseline characteristics of primary efficacy cohort

Demographics	ChAdOx1 nCoV-19 All participants (n=4772)	Control All participants (n=4661)
Age		
18-55 years	3854 (81%)	3796 (81%)
56-69 years	765 (16%)	735 (16%)
≥70 years	153 (3%)	130 (3%)
Sex (female) n%	2657 (56%)	2508 (54%)
BMI (median, IQR) kg/m ²	26 [23, 29]	26 [23, 29]
Ethnicity		
White	3299 (69%)	3254 (70%)
Black	410 (9%)	409 (9%)
Asian	124 (3%)	98 (2%)
Mixed	918 (19%)	874 (19%)
Other	11 (<1%)	12 (<1%)
missing	10 (<1%)	14 (<1%)
Health and social care setting workers n%	3097 (65%)	2974 (64%)
Co-morbidities		
Cardiovascular disease	798 (17%)	782 (17%)
Respiratory disease	491 (10%)	448 (10%)
Diabetes	231 (5%)	185 (4%)

Table 2 Efficacy of 2 doses of ChAdOx1 nCoV-19 against primary symptomatic COVID-19, by SARS-CoV-2 lineage

Lineage	ChAdOx1 nCoV-19	Control	Vaccine efficacy using multiple imputation for missing swabs	
	n (%) N=4772	n (%) N=4661	Vaccine Efficacy (95% CI)	(95% CI)
B.1.1.33	1 (0.0%)	8 (0.2%)	88.2 (5.4, 98.5)	
B.1.1.28	11 (0.2%)	38 (0.8%)	72.6 (46.4, 86.0)	
P.2	38 (0.8%)	115 (2.5%)	68.7 (54.9, 78.3)	64.8 (51.3, 74.5)
P.1	5 (0.1%)	13 (0.3%)	63.6 (-2.1, 87.0)	56.9 (-15.5, 83.9)
Undetermined	22 (0.5%)	48 (1.0%)	56.6 (28.2, 73.8)	

*Undetermined lineage are those where a lineage could not be assigned due to low viral load or degraded RNA.

Table 3 Hospitalisations (WHO score ≥4) by SARS-CoV-2 lineage and WHO clinical progression score

		ChAdOx1 nCoV-19				Control			
WHO clinical progression score		4	5	6	10	4	5	6	10
Secondary cases (> 21 days after dose 1, < 15 days after dose 2)	Undetermined/no swab	0	0	0	0	1	2	0	1
	B.1.1.33	0	0	0	0	1	0	0	0
	P.1	0	0	0	0	1	0	0	0
		0				6			
Primary cases >= 15 days after dose 2	Undetermined/no swab	0	1	0	0	3	3	4	1
	B.1.1.28	0	0	0	0	0	3	1	0
	P.1	0	0	0	0	0	1	0	0
	P.2	0	0	0	0	1	0	1	0
		1				18			
						VE 95% (95% CI 61%, 99%)			

*Undetermined lineage are those where a lineage could not be assigned due to low viral load or degraded RNA.

4=Hospitalised; no oxygen therapy, 5=Hospitalised; oxygen by mask or nasal prongs, 6=Hospitalised; oxygen by NIV or high flow, 10 = dead.

Figures

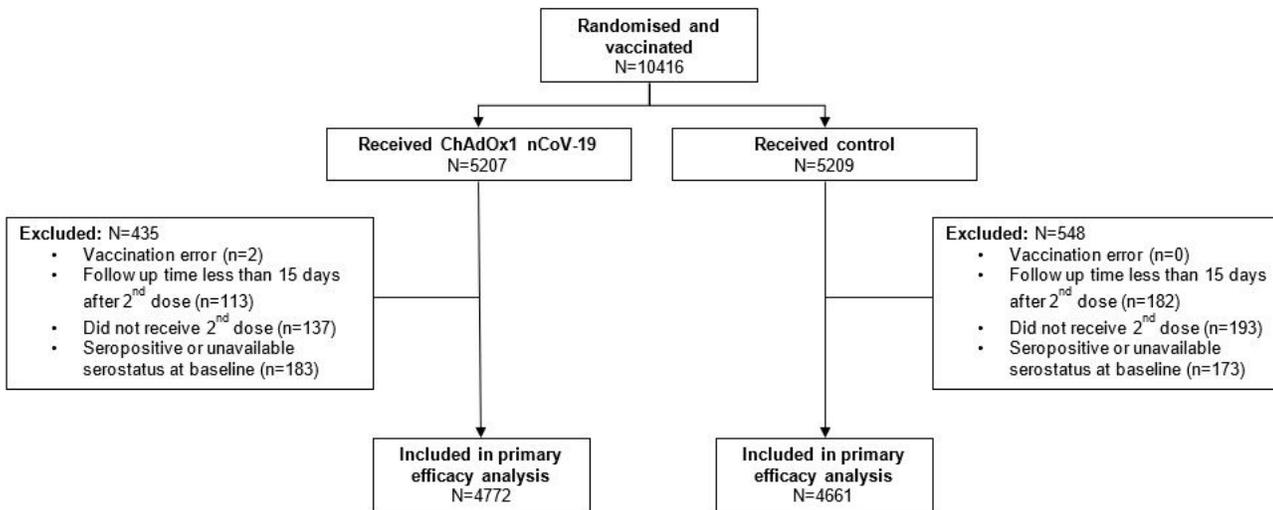


Figure 1

CONSORT

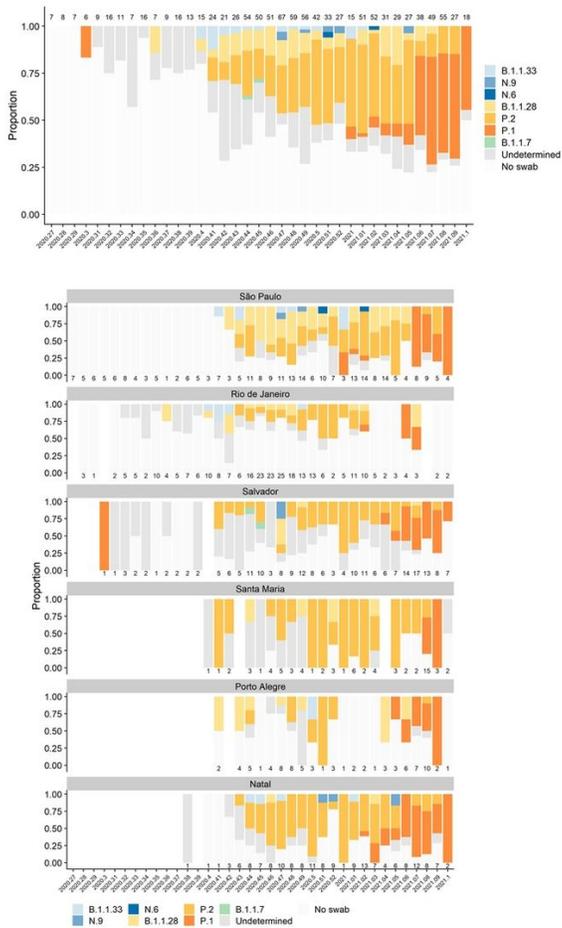


Figure 2

2A PROPORTION OF SARS-COV-2 LINEAGES OVER TIME, An early sample from August 2020 was assigned to P.1 in our dataset due to the presence of K417T. Phylogeographic analyses suggest emergence of the dominant P.1 lineage in November 2020, with a most recent common ancestor of all P.1-like (K417T) viruses estimated at August 2020.⁴⁸ As low viral load of this sample in our dataset precluded sequencing, we were unable to further refine its phylogenetic lineage. Therefore it is plausible that this sample was a precursor to likely 'true' P.1 or a spontaneous K417T mutation. In keeping with national surveillance data, multiple instances of P.1 samples were observed in our data from January 2021. 2B PROPORTION OF SARS-COV-2 LINEAGES OVER TIME – BY SITE No Swab= Participant may have had a PCR test done at a non-study facility and swab was not able to be retrieved, or swab was not stored for study purposes. Undetermined = a lineage could not be assigned due to low viral load or degraded RNA. Weekly numbers below each bar are the total number of cases represented in the figure.

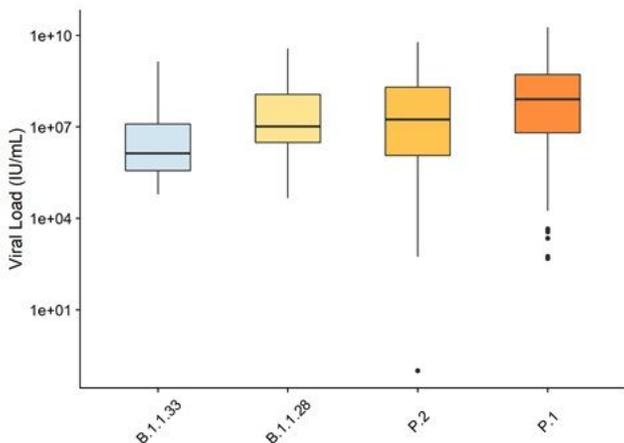


Figure 3

Supplementary Files

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- [BrazilvariantSUPPLEMENTARYMATERIAL1.docx](#)