Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7)

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Summary

Background

A new variant of SARS-CoV-2, B.1.1.7, emerged as the dominant cause of COVID-19 infection in the United Kingdom from November 2020 with a transmission advantage over the previous variants of the virus. Here we report efficacy of the adenoviral vector vaccine, ChAdOx1 nCoV-19, against this variant in comparison with non-B.1.1.7 lineages.

Methods

Volunteers enrolled in phase II/III vaccine efficacy studies in the United Kingdom and randomised 1:1 to receive ChAdOx1 nCoV-19 or a MenACWY control vaccine, provided upper airway swabs every week during the trial and also if they developed possible symptomatic COVID-19 infection. Swabs were tested by nucleic acid amplification test (NAAT) for SARS-CoV-2, and positive samples were sequenced through the COVID-19 Genomics UK consortium (COG UK). NAAT data were used to assess the duration of detectable viral RNA in diagnostic specimens and the viral load. Anti-spike IgG was measured by ELISA at baseline, 14 and 28 days after prime and 28 days after booster vaccination. Neutralising antibody responses were measured using a live virus neutralisation assay against the B.1.1.7 and Victoria lineages of the virus. 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 analysed according to treatment received, with data cut-off on Jan 14, 2021. Vaccine efficacy was calculated as 1 − relative risk derived from a robust Poisson regression model. This study is ongoing and is registered with ClinicalTrials.gov NCT04400838 and ISRCTN 15281137.

Findings

Between 1st October 2020 and 14th January 2021, 499 participants developed Covid-19 infection. 1524 NAAT positive nose/throat swabs were collected from these participants during the trial. Of these, 323 swabs from 256 participants were successfully sequenced. ChAdOx1 nCoV-19 recipients had a significantly lower viral load as represented by minimum PCR Ct value ($p<0.0001$) and were NAAT positive for a shorter time ($p<0.0001$) than participants who received the control vaccine. Virus neutralisation activity by vaccine-induced antibodies was 9-fold lower against the B.1.1.7 variant than against a canonical non-B.1.1.7 lineage. Vaccine efficacy against symptomatic NAAT positive infection was similar for B.1.1.7 and non-B1.1.7 lineages (74.6% [95%CI 41.6-88.9] and 84% [95% CI 70.7-91.4] respectively). There was no difference in anti-spike antibody titres between individuals who had received a prior ChAdOx1 vectored vaccine and those who were naïve to ChAdOx1.

Interpretation

Efficacy of ChAdOx1 nCoV-19 against the B.1.1.7 variant of SARS-CoV-2 is similar to the efficacy of the vaccine against other lineages. Furthermore, vaccination with ChAdOx1 nCoV-19 results in a reduction in the duration of shedding and viral load, which may translate into a material impact on transmission of disease.

Funding

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Research in Context

Evidence before this study

We searched PubMed for research articles published from inception until February 1st, 2021 with no language restrictions, using the terms “SARS-CoV-2” AND “B.1.1.7” OR “VUI-202012/01” OR “VOC-202012/01 OR “Kent”. At the time of the search there were no peer-reviewed publications available on the efficacy of sera from vaccinees to neutralise B.1.1.7 lineage viruses. Pre-print articles have been published using convalescent sera suggest there may be a reduction in neutralisation activity against pseudovirus expressing B.1.1.7 spike protein compared with pseudovirus expressing wild-type spike protein. Preliminary data using sera of vaccinees who were immunised with mRNA vaccines (Pfizer/BioNtech, Moderna) and protein vaccines (Novavax) found either no or modest reduction in neutralisation activity against pseudoviruses containing single mutations found in B.1.1.7 or B.1.1.7 whole spike protein.

Several vaccine developers have published peer-reviewed interim efficacy results against symptomatic Covid-19 disease while others have reported preliminary efficacy results in press releases. At the time of searching there were no peer reviewed publications available on the efficacy of a SARS-CoV-2 vaccine against the lineage B.1.1.7. However, a press release suggests an adjuvanted protein vaccine has vaccine efficacy of 85.6% against the UK B.1.1.7 lineage in a post hoc analysis.

Added value of this study

These are the first published data on the clinical efficacy of a vaccine against SARS-CoV-2 against the novel B.1.1.7 variant compared with non-B.1.1.7 lineages. Vaccine efficacy was preserved against the new variant. Furthermore, vaccination with ChAdOx1 nCoV-19

reduces viral load and length of NAAT positivity against both B.1.1.7 and non-B.1.1.7 lineages.

Implications of all the available evidence

The ChAdOx1 nCov19 vaccine has been given emergency use authorisation in multiple countries including the UK. The B.1.1.7 variant is currently responsible for the majority of disease in the UK. These findings support the ongoing use of ChAdOx1 nCov19 in mass vaccination programmes to both prevent symptomatic B.1.1.7 disease and reduce viral transmission.

Introduction

The SARS-CoV-2 pandemic continues to cause considerable mortality, placing a significant burden on healthcare systems around the world and profound social and economic consequences due to the measures implemented to control the virus. A number of SARS-CoV-2 vaccines have shown efficacy in large-scale Phase 3 trials.[1-6] Whilst the vaccine platforms differ, most utilise the surface spike glycoprotein of SARS-CoV-2 as the key antigenic target for the generation of binding and neutralising antibodies and T cells, and use an antigen coding sequence based on the originally identified Wuhan lineage virus (GenBank accession number M908947). Several vaccines have now been licensed for emergency use by individual countries and large-scale vaccination programs are underway with the anticipation that vaccination will be a key component of future disease control.

As vaccine trials were underway in 2020, novel lineages of SARS-CoV-2 were identified globally,[7-9] often associated with multiple mutations and associated with different epidemiological patterns of infection. New variants are expected to arise to maintain or improve fitness of the virus including transmissibility. In populations with high levels of natural or vaccine-induced immunity, variants that can evade human immune responses are likely to be selected. A novel SARS-CoV-2 variant designated VOC 202012/01 (Variant of Concern, also known as lineage B.1.1.7)[9] was identified in the UK in late 2020 and accounted for an expanding proportion of cases at that time, particularly in the South East and East of England.[9] Whilst most SARS-CoV-2 lineages show relatively few mutations, B.1.1.7 has accrued 23 mutations across the genome including a non-synonymous mutation affecting the spike protein: N501Y, which may increase ACE-2 receptor binding affinity,[10] spike deletion 69-70del associated with viral escape in the immunocompromised[9] and the non-synonymous

mutation P681H affecting the furin cleavage site between S1 and S2 associated with in vitro enhanced membrane fusion of infected cells.[9, 11]

The national community testing system ('Pillar 2') in the UK is delivered by a limited number of large laboratories, many of which are using a ThermoFisher TaqPath 3-gene PCR assay. The 69-70 deletion means that the S gene qPCR probe cannot bind and is recognised to cause S gene target failure (SGTF).[12] Whilst other variants can contain this mutation, since 30 November 2020, 96% of all UK Pillar 2 69-70del sequences were due to the B.1.1.7 lineage,[13] permitting the use of the PCR result to act as a proxy marker for this variant during this timeframe.[14, 15] Indirect associations between SGTF, or mutations present in B.1.1.7 and higher viral loads[16, 17] and transmission[14] have already been demonstrated. B.1.1.7 may present a R_0 that is 1.75 higher than lineages without the N501Y mutation[18] and UK public health measures in place to control the virus failed to control spread of this lineage but were effective for those lineages without S gene target failure.[14] Several unpublished independent analyses suggest that infections caused by isolates which show SGTF may be associated with an increased fatality rate.[19]

The advent of a variant with multiple mutations also raises concerns regarding the efficacy of natural infection-derived immunity to prevent reinfection as well as vaccine efficacy. Assessing immune evasion in vivo by B.1.1.7 is challenging given the timing of the emergence of this variant (approximately 8 months after the first wave in the UK) combined with the finding in healthcare workers that following primary infection the observed median protective effect was at least five months,[20] though reinfection with B.1.1.7 and subsequent critical illness has been reported.[21]

Amino acid 501 of SARS-CoV-2 spike protein sits within the receptor binding domain (RBD) of the S1 subunit. The RBD binds to ACE2 receptors and permits viral entry into host cells and is a key target for neutralising antibodies. Neutralising antibodies out-compete binding to the RBD thereby preventing infection from both pseudo- and wild-type virus.[22] Encouragingly early *in silico* analysis suggests that the mutations present in B.1.1.7 may only confer limited changes in epitope signal.[23] Early studies assessing the neutralizing ability of sera from convalescent patients and vaccinees against pseudoviruses expressing some mutations present in B.1.1.7 or the entire B.1.1.7 spike protein suggest no or limited reduction in neutralisation.[24-28] Early reports suggest that vaccine efficacy may not be reduced in the face of this variant.[4]

The new variant in the UK arose while there was a low level of population immunity from natural infection and before vaccine programmes had been rolled out, and so the variant is likely to have been selected for through improved ACE2 receptor binding and transmissibility rather than as a result of vaccine-induced immunity. Furthermore, multiple epitopes are recognised by neutralising antibody and other antibody functions[29] and may involve binding to non-RBD epitopes in spike protein, which may provide protection even with the presence of the mutations recognised in B.1.1.7. T cell responses may also provide protection against infection and have been demonstrated following vaccination with the mRNA[30, 31] and viral vector vaccines[32] that are currently available in the UK.

Previously we reported the efficacy of the simian adenoviral vectored vaccine ChAdOx1 nCoV-19 (AZD1222) from randomised controlled trials in Brazil and the UK[3] from analyses done prior to the spread of the B.1.1.7 variant across the UK. In this report we provide both an in vitro analysis of vaccine induced neutralising antibody responses against B.1.1.7 and an

analysis of the clinical efficacy of ChAdOx1 nCoV-19 against disease caused by the B.1.1.7 VOC using data from the UK. As novel variants are identified, new targeted vaccines may need to be implemented in future public health programmes as booster doses. We also present data on the immune response to ChAdOx1 nCoV-19 in participants who previously received other ChAdOx1 vectored vaccines.

Methods

In this ongoing, single-blind multicentre randomised phase II/III trial (COV002), the safety and efficacy of the ChAdOx1 nCoV-19 vaccine is being assessed in adults aged 18 and over at 20 centres in the UK. Safety, immunogenicity and efficacy data, including the full protocol and statistical analysis plan have been previously published in detail.[3, 29, 33, 34] Briefly, participants were randomised to receive standard dose ChAdOx1 nCoV-19 vaccine or group A,C,W,Y meningococcal vaccine (MenACWY) as control. A subset of participants received a low dose vaccine as their first dose. The primary outcome was symptomatic COVID-19 infection defined as a positive nucleic acid amplification test (NAAT+) on a nose or throat swab in a participant with at least one symptom including cough, fever > 37.8ºC, shortness of breath, anosmia or aguesia.

The ChAdOx1 nCoV-19 vaccine was licensed for use in the UK on 30th December 2020 with priority groups such as older adults and frontline health care workers targeted for vaccination first. The majority of participants in the trial were recruited from these high-exposure populations and were therefore eligible for vaccination under the government NHS coronavirus vaccine programme. Participants who were offered vaccination through the government programme were unblinded individually. Cases occurring after a participant was unblinded are not included in this report and these participants are censored in the analysis at the time of unblinding.

The study was sponsored by the University of Oxford (Oxford, UK) and approved in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA) reference 21584/0428/001-0001 and the South-Central Berkshire Research Ethics Committee reference 20/SC/0179. Safety data was reviewed regularly by an independent data safety monitoring board.

Participants were reminded weekly by email or text message to contact the trial team if they developed COVID-19 primary outcome symptoms. Participants who met criteria for symptomatic testing underwent clinical assessment and nasopharyngeal and oral swabbing at their local clinical site. Samples were processed using MHRA-derogated NAAT assays within UKAS-accredited NHS diagnostic laboratories for each study site.

Additionally, participants were asked to provide a weekly self-administered nose and throat swab for NAAT testing from 1 week after first vaccination using home test kits provided by the Department of Health and Social Care (DHSC).[3] Symptoms in these participants were not routinely assessed as swabs were done at home and sent for testing through the post. Home testing kits were processed at DHSC designated laboratories. The Glasgow Lighthouse Laboratory, Milton Keynes Lighthouse Laboratory and Alderley Park Lighthouse Laboratory processed the majority of trial swab samples (98.3% to 14th January 2021) and exclusively used the Thermofisher TaqPath™ assay (target genes ORF1ab, S, N) for viral detection. Participants were directly informed of their results by text and email from the National Health Service (NHS). Swab results from trial barcoded swabs were provided to the trial team by NHS Digital.

SARS-CoV-2 RNA from home testing kits was identified at the Glasgow, Alderley Park and Milton Keynes Lighthouse laboratories and sent for sequencing. SARS-CoV-2 RNA from 15 of the 19 site diagnostic laboratories was obtained. Samples were batched at point of testing,

and consolidated batches sent for sequencing and genome assembly to COG-UK partner laboratories. The majority of samples (70%) during the study period were generated by Oxford Viromics (Wellcome Centre for Human Genetics, University of Oxford) using the quantitative veSEQ approach. For a full description of the sequencing protocol see [35, 36]. Briefly, unique dual indexed (UDI) libraries were constructed using the SMARTer Stranded Total RNA-Seq Kit v2—Pico Input Mammalian (Takara Bio USA, California, USA) with no RNA fragmentation. An equal volume of library from each sample was pooled for capture, and size-selected to exclude fragments shorter than 400nt. Target enrichment of SARS-CoV-2 was carried out with a custom xGen Lockdown Probes panel (IDT, Coralville, USA), using the SeqCap EZ Accessory Kits v2 and SeqCap Hybridization and Wash Kit (Roche, Madison, USA) for hybridization of the probes and removal of unbound DNA. Following 12 cycles of PCR for post-capture amplification, the final product was purified using Agencourt AMPure XP (Beckman Coulter, California, USA). Sequencing was performed on the Illumina NovaSeq (Illumina, California, USA) at the Oxford Genomics Centre (OGC), generating 250bp paired-end reads. Each sequencing batch of up to 96 samples included a non-SARS-CoV-2 in-run control (purified in vitro transcribed HIV RNA from clone p92BR025.8, obtained from the National Institute for Biological Standards and Control (NIBSC)), as well as positive and negative quantification controls consisting of in vitro transcribed SARS-CoV-2 RNA (Twist Synthetic SARS-CoV-2 RNA Control 1 (MT007544.1), Twist Bioscience) diluted into Universal Human Reference RNA (UHRR) to a final concentration of SARS-CoV-2 RNA of 500,000, 50,000, and 0 copies/reaction. Controls were checked to ensure no evidence of amplification in the negatives and expected RNA quantification consistent with Ct values provided by the testing laboratories.

Viral genomes were assembled as previously described [35] and variant frequencies were computed using shiver [37] (tools/AnalysePileup.py), with the default settings of no BAQ and

maximum pileup depth of 1000000. Lineages were assigned by the Pangolin web server (https://pangolin.cog-uk.io v2.1.7, lineages version 2021-01-20) using the determined consensus genome for each sequenced sample. Consensus sequences were aligned using MAFFT v7.402.[38] Phylogenetic reconstruction was performed on the alignment consisting of consensus sequences rooted with the Wuhan-Hu-1 reference sequence (RefSeq NC_045512), using IQTREE v1.6.12[39] with the GTR+F model and 1000 bootstrap replicates.

Sera from vaccinated participants were tested using a live SARS-CoV-2 microneutralisation assay (ND_{50}), at Public Health England (Porton Down, UK), as described previously [33]. The B.1.1.7 lineage and a canonical non-B.1.1.17 Victoria lineage (NIBSC, BetaCoV/Australia/VIC01/2020) were used in neutralising assays.

Humoral responses at baseline and after vaccination in recipients of a different previous ChAdOx1 vaccine were assessed using a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein as previously described.[33]

Cases were included in efficacy analyses from randomised participants enrolled in efficacy cohorts, that occurred between October 1st, 2020 and January 14th, 2021 and sequencing results from at least one swab were available. Both those receiving two standard doses (SD/SD), or a low dose followed by a standard dose (LD/SD) are included. Cases were excluded if they occurred before 15 days post the second dose of vaccine or occurred in participants who were not seronegative on a SARS-CoV-2 N protein assay at baseline. Participants who were unblinded in order to receive a vaccine through the government COVID-19 vaccination scheme were censored in the analysis on the day of their unblinding.

All endpoints were reviewed for inclusion by an independent blinded adjudication committee.

Vaccine efficacy was calculated as 1- the relative risk calculated from a robust Poisson model in SAS version 9.4. The model contained terms for treatment group and vaccine group

(LD/SD or SD/SD). The logarithm of the period at risk was used as an offset variable in the model to adjust for volunteers having different follow up times during which the events occurred.

To determine if vaccination with ChAdOx1 nCoV-19 was associated with reduced viral load and/ or reduced number of weeks of NAAT positivity, PCR Ct values as a proxy for viral load, were analysed from weekly swabs processed in lighthouse laboratories. The minimum Ct value across the N and ORF1ab genes from each PCR test was computed for each swab and the minimum Ct value across all positive swabs was compared between vaccine groups using a Wilcoxon Rank Sum test.

Neutralising titres from a live-virus microneutralisation assay were available from sera tested against both the B.1.1.7 lineage and the Victoria lineage. The geometric mean ratio (B.1.1.7/Victoria) was computed to show the change in neutralising potential with the different lineage, and $\log_2$-titres compared using a paired t-test.

Anti-SARS-CoV-2 spike antibody titres in those who had received a previous different ChAdOx1 vaccine were compared with those who received two standard doses of ChAdOx1 nCoV-19 at 14 and 28 days after the first dose, and 28 days after the second dose using Wilcoxon Rank Sum test.

Baseline characteristics were compared between those with B.1.1.7 vs non-B.1.1.7 variants using Chi-squared and Fisher Exact tests for binary variables, a Wilcoxon Rank Sum tests for BMI, and Cochran-Armitage tests for ordinal age groups and prime-boost intervals.

Role of the funding source

AstraZeneca reviewed the data from the study and the final manuscript before submission, but the academic authors retained editorial control. All other funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 1st October 2020 and 14th January 2021, 499 participants developed Covid-19 infection. 1524 NAAT positive nose/throat swabs were collected from these participants during the trial. Sequences were available from 323 of these swabs, representing 256 participants. 179 of these cases occurred in participants in the primary efficacy cohort and prior to unblinding, of which 120 were cases of primary symptomatic COVID-19 and 44 were asymptomatic or had unknown symptoms (Figure 1).

For primary symptomatic cases in which sequence data were available 34 (28.3%) were due to the B.1.1.7 variant and 86 (71.7%) were caused by non-B.1.1.7 lineages. Asymptomatic infections or those with unknown symptoms were similarly distributed with 14 (32%) infections due to the B.1.1.7 variant and 30 (68%) due to non-B.1.1.7. Sequenced lineages are shown in Figure 2. Cases of B.1.1.7 first arose in late November in trial sites in London and formed an increasing proportion of positive swabs during December and January as shown in Figure 3.

Vaccine efficacy against primary symptomatic B.1.1.7 disease was 74.6%, 95% CI 41.6%, 88.9%, similar to efficacy seen against symptomatic non-B.1.1.7 disease of 84.1%, 95% CI

70.7%, 91.4%. For cases of asymptomatic/unknown symptom infection obtained from weekly self-swabs, vaccine efficacy was higher for non-B.1.1.7 infections 75.4%, 95% CI 39.9%, 89.9% than for B.1.1.7 26.5% 95% CI, -112.0%, 74.5%, although fewer cases were available for analysis, so confidence intervals are wide and overlapping. In contrast, no efficacy was seen for asymptomatic/unknown infections that were not sequenced 3.1%, 95% CI, -37.3%, 31.6%. Overall efficacy against the B.1.1.7 variant from all cases was 66.5% 95% CI, 37.1%, 82.1%, compared with 80.7% 95% CI, 69.2%, 87.9% against other variants (Table 1). Baseline demographics in those with B.1.1.7 variant were similar to those with non-B.1.1.7 variants, as were their prime-boost intervals (Table S1).

There were 21 (62%) cases of primary symptomatic B.1.1.7 variant COVID-19 in those who received SD/SD vaccines, and 13 (38%) occurred in the LD/SD group. Similarly, non-B.1.1.7 variant cases of primary symptomatic COVID-19 were distributed with 63% in the SD/SD group and 37% in the LD/SD group. Efficacy was very similar in the SD/SD group as the LD/SD group for B.1.1.7 (76.5% vs 71.3% for SD/SD and LD/SD respectively), and for non-B.1.1.7 cases (82.7% vs 86.3% for SD/SD and LD/SD. When broken down by SD/SD and LD/SD groups few cases were available for robust comparisons for asymptomatic/unknown infections (Table S2).

Minimum Ct values (an inverse proxy for peak viral load) from Lighthouse lab swabs in ChAdOx1 nCoV-19 vaccinated participants were higher than in those who received the control vaccine ($p<0.0001$) and participants were PCR-positive for a shorter period of time ($p<0.0001$). Primary symptomatic cases had lower Ct values than asymptomatic/unknown symptom cases ($p<0.0001$) and were PCR positive for a longer period of time ($p<0.0001$). (Figures 4 and 5). Almost all (79%) asymptomatic participants returned only one positive swab. However, primary symptomatic cases remained PCR positive for longer with only 21%

returning only a single positive swab. Vaccination reduced the median length of time positive by 1 week (median 1.0 week IQR 1.0, 2.0 ChAdOx1 nCoV-19, and median 2.0 weeks IQR 1.0, 3.0 MenACWY). The number of weeks positive in cases identified as B.1.1.7 variant was not different to the non-B.1.1.7 variant cases (P=0.5202), Table S3

In a live viral neutralisation assay, neutralising titres from ChAdOx1 nCoV-19 recipients were 9-fold lower against the B.1.1.7 lineage than against the Victoria lineage (GMR 8.9, 95% CI 7.2, 11.0) (Figure 6).

Using an ELISA that detected total IgG against trimeric spike protein, we observed that participants who had previously received a different ChAdOx1-vector vaccine had similar anti-spike antibody titres at all timepoints after vaccination as ChAdOx1-naïve individuals (Figure S1, Table S4).

Discussion

Our findings show that while measured neutralising antibody titres generated by vaccination with ChAdOx1 nCoV-19 vaccine are lower for the B.1.1.7 lineage, clinical efficacy of the vaccine against symptomatic COVID disease is similar between B.1.1.7 and non-B.1.1.7 lineages with overlapping confidence intervals. These findings suggest that either lower neutralising antibody titres are sufficient to provide protection or that other mechanisms of immunity may be responsible for protection from disease in vaccinated individuals. The protection against this new variant, described here, is an important finding for regions where B.1.1.7 is now the dominant variant and vaccine programmes are already underway.

However, it should be noted that further mutations in spike protein observed in other novel lineages[7, 8] appear to be driven by escape of the virus from the neutralising activity of public antibodies[40-42], indicating that prevention of transmission may be temporary as the virus adapts to natural and/or vaccine-induced immunity.

The presence of viral RNA in a diagnostic swab may not represent transmissible live virus. However, studies using different PCR platforms have shown that infectious virus was not isolated from patients with a Ct value greater than 24[43] or with fewer than 6.63 $x10^{10}$ RNA copies/ml.[44] Previous studies have shown no difference in viral load between symptomatic and asymptomatic individuals.[45] In our study, individuals who did not report symptoms had lower viral loads than symptomatic individuals and were NAAT positive for a shorter period of time. This is consistent with published data that asymptomatic individuals may be responsible for fewer secondary transmissions than symptomatic individuals.[46]

The viral load among those with a PCR positive swab in the ChAdOx1 nCoV-19 vaccinated group was significantly lower than among those who were in the control group. Taken with our recent analysis,[47] which showed a 67% reduction in any PCR positive result after a single dose of ChAdOx1 nCoV-19, our findings suggest that even those vaccinees with a PCR-positive swab may be less likely to transmit the virus than an unvaccinated PCR-positive individual. These observations provide strong support for mass vaccination as a tool to control pandemic coronavirus.

Vaccine efficacy against asymptomatic infection using sequenced swabs was high (75%) for non-B.1.1.7 variants, higher than our previously published estimate of 27% which was based on NAAT positivity alone,[3]and substantially higher than the efficacy seen in those asymptomatic cases that are not yet sequenced (3%), or in those for whom no result from sequencing could be obtained (-29%). As false positive samples cannot be sequenced, any false positives would fall into the category with -29% efficacy, along with those with very low viral loads or degraded RNA. These contrasting results are notable and point to the potential for false-positive PCR results from weekly swabbing. In our study, more than

200,000 nose and throat swabs from participants self-swabbing at home have been NAAT+ tested. Assuming a low false positive rate of 0.1% this equates to 200 false positive swabs, which could skew an attempt to estimate vaccine efficacy. The higher estimate of efficacy against asymptomatic infection in this study from sequenced swabs is an estimate free of the dilution caused by false positive results and therefore may be more reliable. However, inflated efficacy against asymptomatic infection may also be caused by lower viral loads in the samples from vaccine recipients making sequencing more difficult for these samples, thereby lowering the counts in the vaccine arm of the study and inflating VE for asymptomatic infections. This bias would be unlikely to affect primary symptomatic cases where viral loads are higher.

Sequence data were obtained from swabs performed on symptomatic participants at local trial sites and from weekly surveillance swabs. Where swabs were available for sequencing, the lineage distribution of trial isolates closely followed the overall trend across the UK,[13] with an increasing dominance of B.1.1.7 isolates from late-November 2020. While the overall numbers of positive participants are small, this suggests that there has been no vaccine-driven selection on infection caused by B.1.1.7 within the trial.

Paired comparison of neutralising antibody activity of sera from ChAdOx1 nCoV-19 vaccinees showed reduced activity against the B.1.1.7 lineage compared with a canonical non-B.1.1.7 lineage (Victoria). The Victoria lineage is phylogenetically similar to the original Wuhan outbreak lineage and has only a single mutation in spike protein (S247R). Vaccine sera from the Pfizer BNT162b2 mRNA recipients show no change in neutralising activity using pseudovirus assays comparing a VSV expressing B.1.1.7 or ancestral Wuhan lineage spike protein.[26] Sera from recipients of the Moderna mRNA-1273 vaccine also showed similar neutralising activity against VSV and lentivirus pseudoviruses expressing full spike

protein from either B.1.1.7 or a Wuhan lineage.[48] However, a live coronavirus neutralisation assay showed both BNT162b2 vaccinee sera and ChAdOx1 nCoV-19 vaccinee sera had a 3-fold reduction in neutralisation activity against B.1.1.7, when compared with the Victoria lineage[42] in keeping with our findings. These apparently different results with neutralising antibody assays using pseudoviruses and live virus highlight the need for caution in interpretation of viral neutralisation data.

Despite the reduction in measured live neutralising activity of sera from ChAdOx1 nCoV-19 recipients, in this study efficacy of the vaccine after a second dose was preserved against B.1.1.7 with overlapping confidence intervals and was similar to our previously published efficacy results from cases accrued prior to the emergence of B.1.1.7.[3, 47] An adjuvanted spike protein-based vaccine, Novavax NVX-CoV2373, has also recently reported preliminary findings of similar clinical efficacy against symptomatic COVID-19 disease between B.1.1.7 and non-B.1.1.7 lineages.[4] This vaccine is also based on the Wuhan lineage spike gene sequence, which supports our finding that immune responses elicited by ancestral spike protein offer a degree of cross-protection against the B.1.1.7 lineage.

Pre-clinical COVID vaccine studies suggest that development of neutralising antibody is associated with protection from subsequent challenge with live virus.[49] In the absence of a formal correlate of protection, vaccine developers have therefore measured neutralising antibody titres post vaccination as a surrogate of likely efficacy. Our findings that ChAdOx1 nCov-19 offers similar protection against B.1.1.7 lineages may mean that a lower absolute level of neutralising antibody is needed to prevent symptomatic infection.

Different functional Fc-mediated humoral mechanisms may also be responsible for protection afforded by ChAdOx1 nCoV-19. Antibody-dependent complement deposition (ADCD) and Antibody-dependent Natural Killer cell activation (NKA) are associated with protection from challenge in animal models.[50] We have previously demonstrated that ChadOx1 nCoV-19 elicits robust antibody-dependent monocyte phagocytosis (ADMP), antibody-dependent neutrophil phagocytosis (ADNP) activity and ADNKA after 2 doses of vaccine,[29] at similar levels to that seen in convalescent sera. B. Antibodies mediating these functions may have complementarity determining regions that recognise and bind to alternative conformational epitopes on spike protein to neutralising antibodies, explaining the observed maintained clinical efficacy against B.1.1.7.

T cell responses are associated with recovery from clinical COVID infection[51] and we have previously reported that ChAdOx1 nCoV-19 generates spike specific T cells which peak at 14 days after priming vaccination.[34] Network analysis of conserved T cell spike protein epitopes show the majority of these linear peptides are derived from regions of the protein critical for maintaining protein structure and therefore less likely to be subject to immune selection pressure.[52] We have previously shown that the peptide pools most frequently recognised by vaccine elicited T cells span amino acids 311–430 and 101–200 of the S1 domain which are unaffected by the mutations seen in B.1.1.7. This supports the likelihood that cellular immune responses to ChAdOx1 nCoV-19 are sustained against the new variant independently of neutralising activity. Further evaluation of the cross-reactivity of vaccine derived T cell clones to B.1.1.7 spike peptides is under way.

Since December 2020, regulatory authorities around the world have approved emergency use of several COVID 19 vaccines as part of the strategy to combat COVID-19 disease. As of 31st January, 8.9 million people have been immunised in the UK.[53] As an increasing proportion of the population is vaccinated, selection of mutations that allow immune evasion may occur requiring re-vaccination with antigens derived from the new lineages. Concerns exist that repeated doses of adenoviral vaccine vectors may generate anti-vector immunity which may impede responses to the pathogen transgene. We have previously shown that anti-ChAdOx1 vector antibodies do not impact on anti-spike antibody responses or spike specific T cell responses.[34] Here we demonstrate that individuals who have received a prior ChAdOx1-vectored vaccine for a non-spike transgene at least one year prior to receipt of ChAdOx1 nCoV-19 have similar binding antibody responses to spike protein compared to ChAdOx1-naïve individuals. However, the impact on transgene responses of, for example, an annual vaccination with the same adenoviral vector remains uncertain and heterologous prime-boost strategies incorporating different vaccine platforms may be required.

A limitation of this study is that sequences from all positive swab samples could not be obtained due to logistical constraints in laboratories processing multiple clinical samples during the COVID pandemic. While human error in the receiving and sequencing laboratories and missteps in quality control of data matching between laboratories could have impacted on data veracity, in most cases multiple swabs were obtained from the same individual over a period of weeks, allowing corroboration of in-host minor variants, and providing certainty of sequence linkage to a given participant. The sequences obtained for this study were generated by multiple sequencing laboratories affiliated with the COVID19 Genomics UK (COG-UK) Consortium, using local infrastructure for library preparation and sequencing, with independent quality control procedures performed at each sequencing site

and centrally within COG-UK. The use of heterogeneous sequencing data from high-throughput processes warrants some caution in the interpretation of consensus genomes. Only genomes that had no evidence of contamination were included in this analysis, with sequences showing evidence of mixed variant calls at lineage defining sites being manually excluded. Furthermore, samples with a high Ct value (>30) were not routinely sequenced by several COG UK laboratories, thus limiting our ability to assess the lineage of low viral load specimens, which were overrepresented in asymptomatic participants. Participants in the trial will continue to provide weekly swabs until June 2021. As further data accumulate, it may be possible to make more detailed analyses of efficacy against B.1.1.7 and other emerging novel variants.

Ultimately, the emergence of new lineages of SARS-CoV-2 due to viral mutation and immune and fitness selection is inevitable. Here, we show that the clinical efficacy of the ChAdOx1 nCoV-19 vaccine against the novel B.1.1.7 lineage is similar to efficacy results described with SARS-CoV-2 lineages circulating in the UK at an earlier timepoint in the pandemic. Vaccination with ChAdOx1 nCoV-19 also results in a reduction in the duration of shedding and viral load, which may reduce transmission of disease, supporting the ongoing use of this vaccine to protect populations at risk of disease.

Contributors

AJP and SCG conceived the trials and AJP is the chief investigator. AJP, DJ, KRWE, MNR, MV, PF, TG and TL contributed to the protocol and design of the study. AC, CJAD, SNF, AF, ALG, CAG, PH, HCH, RL, VL, PJL, AM, KMP, AS, RKS, ECT, MT, DPJT, CJW, AVSH and MNR are study site principal investigators. PKA, EP, DJ, PMF, SB, KJE, JH, MF, TC, AMM, BA, PC, SK, YFM, RS, MDS, TLV, AF, DB and BH contributed to the implementation of the study or data collection. DJP, SF, MG, NGM, and MV did the

statistical analysis. CMG and ADD were responsible for vaccine manufacturing. AJP, DJP, 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. TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and was consultant to Vaccitech. 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 and SNF are NIHR Senior Investigators. AVSH is a cofounder of and consultant to Vaccitech and is named as an inventor on a patent covering design and use of ChAdOx1-vectored vaccines (PCT/GB2012/000467). MDS reports grants from Janssen, GlaxoSmithKline, Medimmune, Novavax, and MCM Vaccine and grants and non-financial support from Pfizer outside of the submitted work. CG reports personal fees from the Duke Human Vaccine Institute outside of the submitted work. ADD reports grants and personal fees from AstraZeneca outside of the submitted work. SNF reports grants from Janssen and Valneva, outside the submitted work. TLV and JV are employees of AstraZeneca. All other authors declare no competing interests.

The views expressed in this publication are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

Figures

Figure 1. CONSORT diagram of sequences included in the analysis

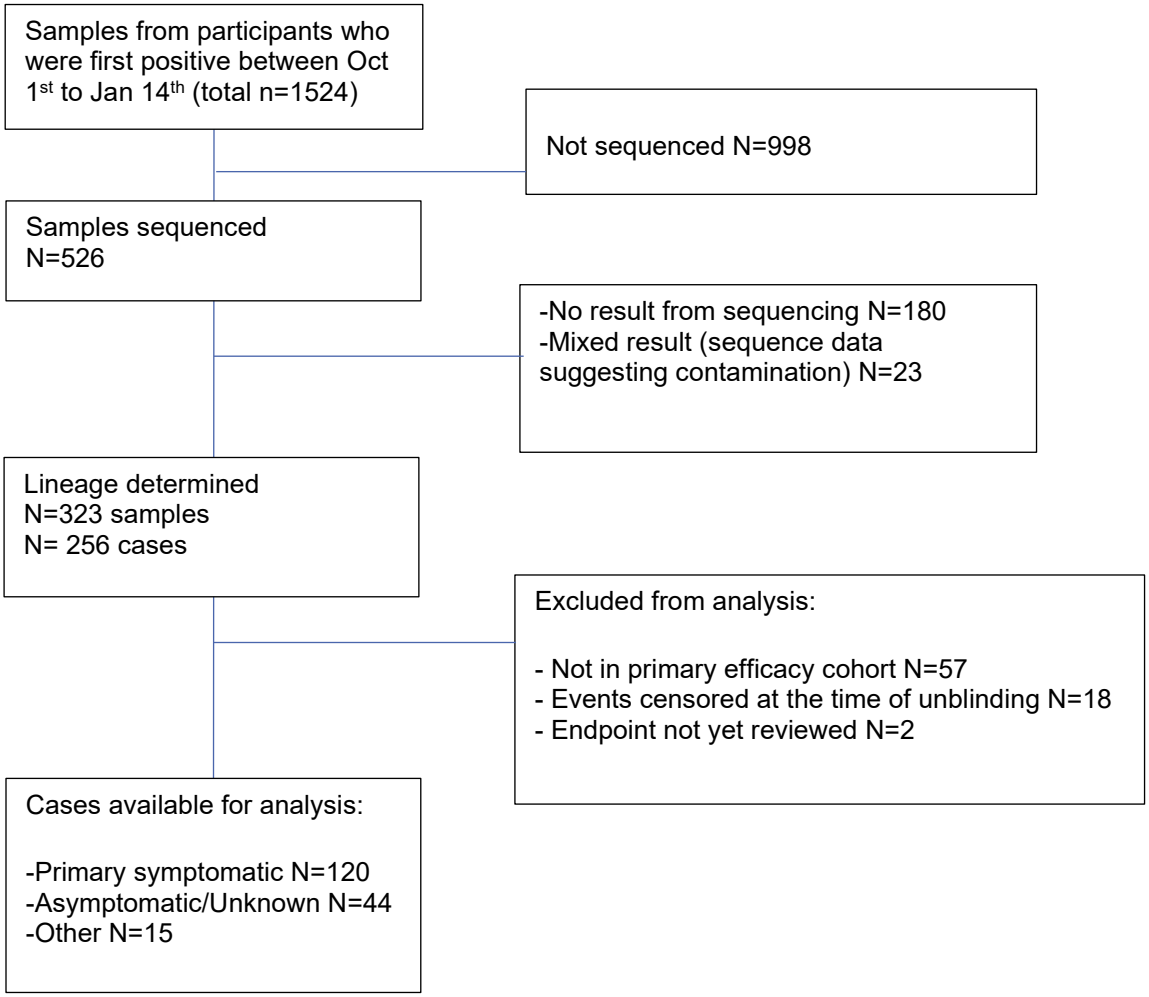
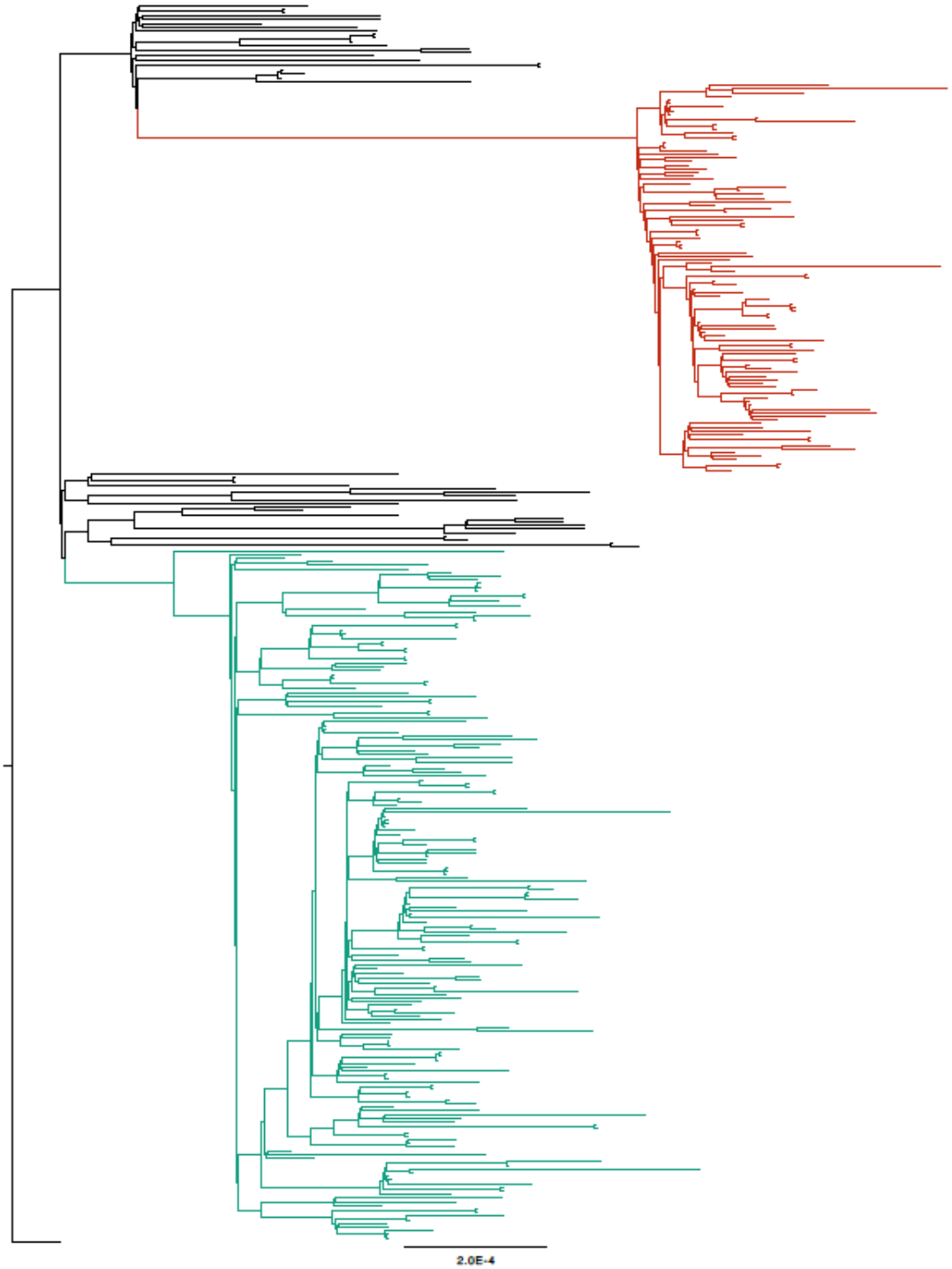


Figure 2. Consensus phylogeny of SARS-CoV-2 genomes identified in this study



Clades are coloured by variant lineage: red, B.1.1.7; green, B.1.177 (most common UK variant during the study period); black, other lineages. n=340. Lineages assigned by Pangolin v2.1.7, lineages version 2021-01-20).

Figure 3 Cumulative number of B.1.1.7 lineage and non-B.1.1.7 lineage isolates identified between October 1st 2020 and January 14th 2021

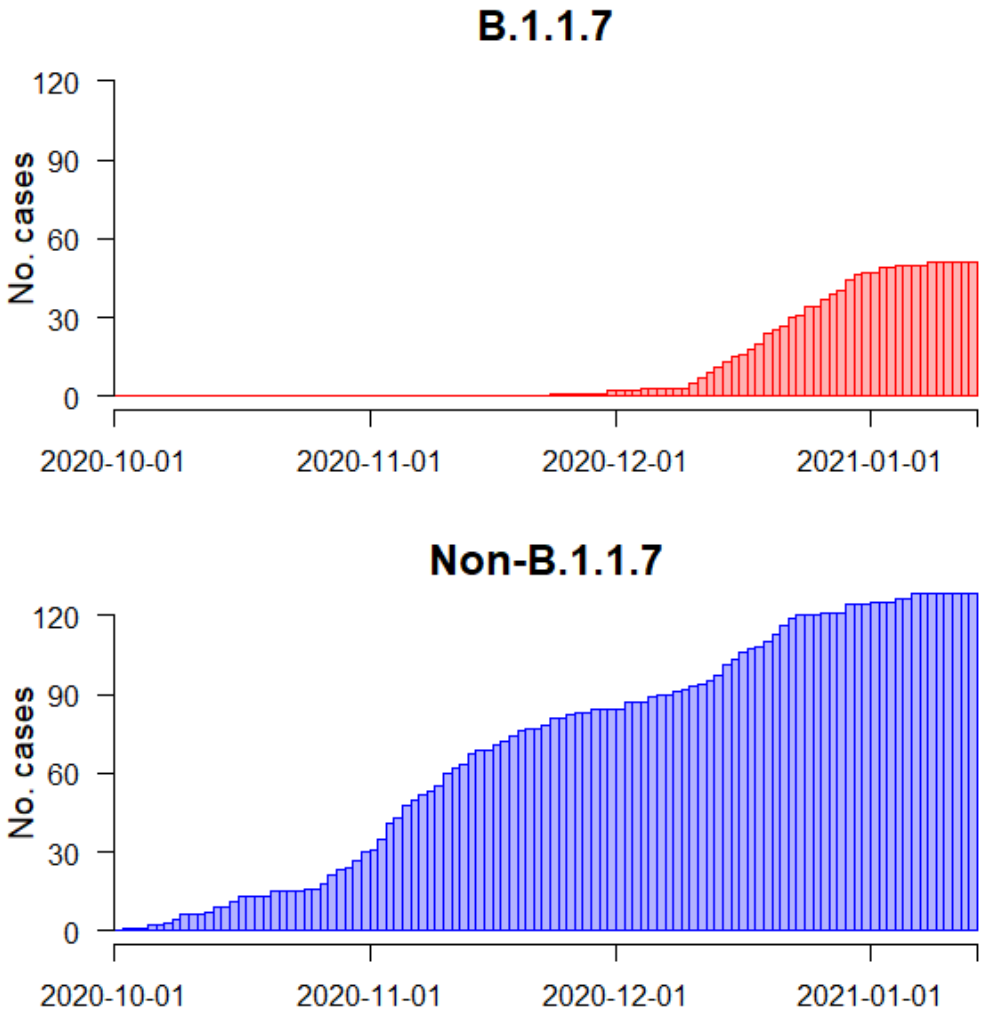


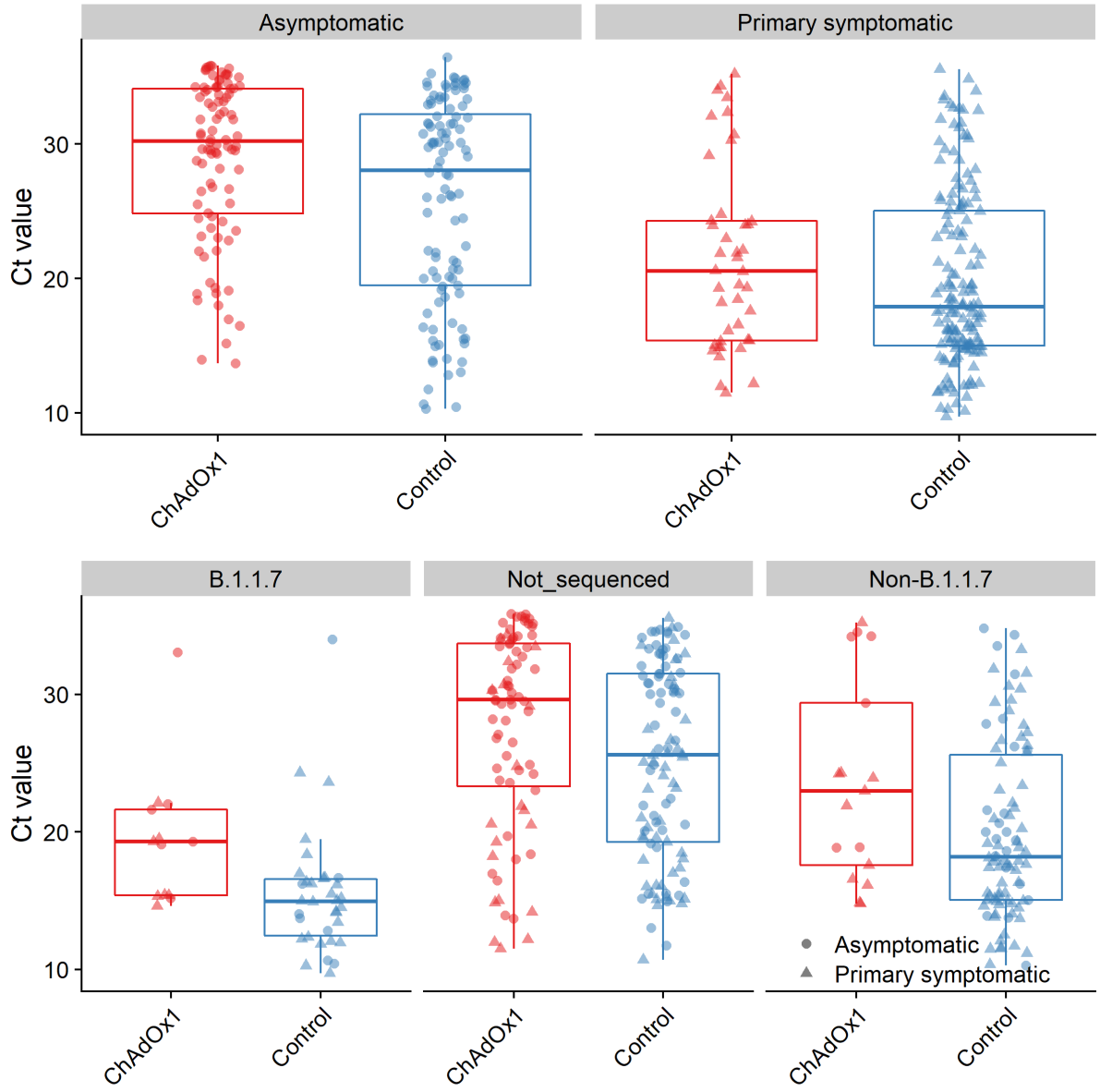
Table 1 Vaccine efficacy against B.1.1.7 and non- B.1.1.7 strains. (SD/SD and LD/SD seronegative efficacy cohorts only)

	Variant	N (%)	ChAdOx1 nCoV-19	Control	VE 95%CI
Primary Symptomatic COVID-19					
	B.1.1.7	34 (14%)	7/4236	27/4270	74.6% (41.6%, 88.9%)
	Other variants	86 (34%)	12/4236	74/4270	84.1% (70.7%, 91.4%)
	No sequence result*	25 (10%)	5/4236	20/4270	75.4% (34.3%, 90.8%)
	Not sequenced**	105 (42%)	28/4236	77/4270	64.3% (44.9%, 76.8%)
	Total cases	250	52/4236	198/4270	74.2% (65.0%, 81.0%)
Asymptomatic/Unknown infections					
	B.1.1.7	14 (7%)	6/4236	8/4270	26.5% (-112.0%, 74.5%)
	Other variants	30 (14%)	6/4236	24/4270	75.4% (39.9%, 89.9%)
	No sequence result	37 (18%)	21/4236	16/4270	-28.7% (-146.6%, 32.8%)
	Not sequenced	127 (61%)	63/4236	64/4270	3.1% (-37.3%, 31.6%)
	Total cases	208	96/4236	112/4270	15.7% (-10.7%, 35.8%)
Any NAAT+ infection†					
	B.1.1.7	51 (10%)	13/4236	38/4270	66.5% (37.1%, 82.1%)
	Other variants	128 (26%)	21/4236	107/4270	80.7% (69.2%, 87.9%)
	No sequence result	69 (14%)	29/4236	40/4270	28.8% (-14.9%, 55.9%)
	Not sequenced	251 (50%)	101/4236	150/4270	33.8% (14.7%, 48.6%)

	Total cases	499	164/4236	335/4270	51.9% (42.0%, 60.1%)

*no viable sequence obtained or unprocessed due to CT >30, **sample did not enter sequencing pipeline or was destroyed. † includes primary symptomatic cases, non-primary symptomatic cases (those with other symptoms such as nausea or diarrhoea), asymptomatic cases and cases where symptoms were unknown.

Figure 4 Minimum Ct values across all PCR positive swabs†

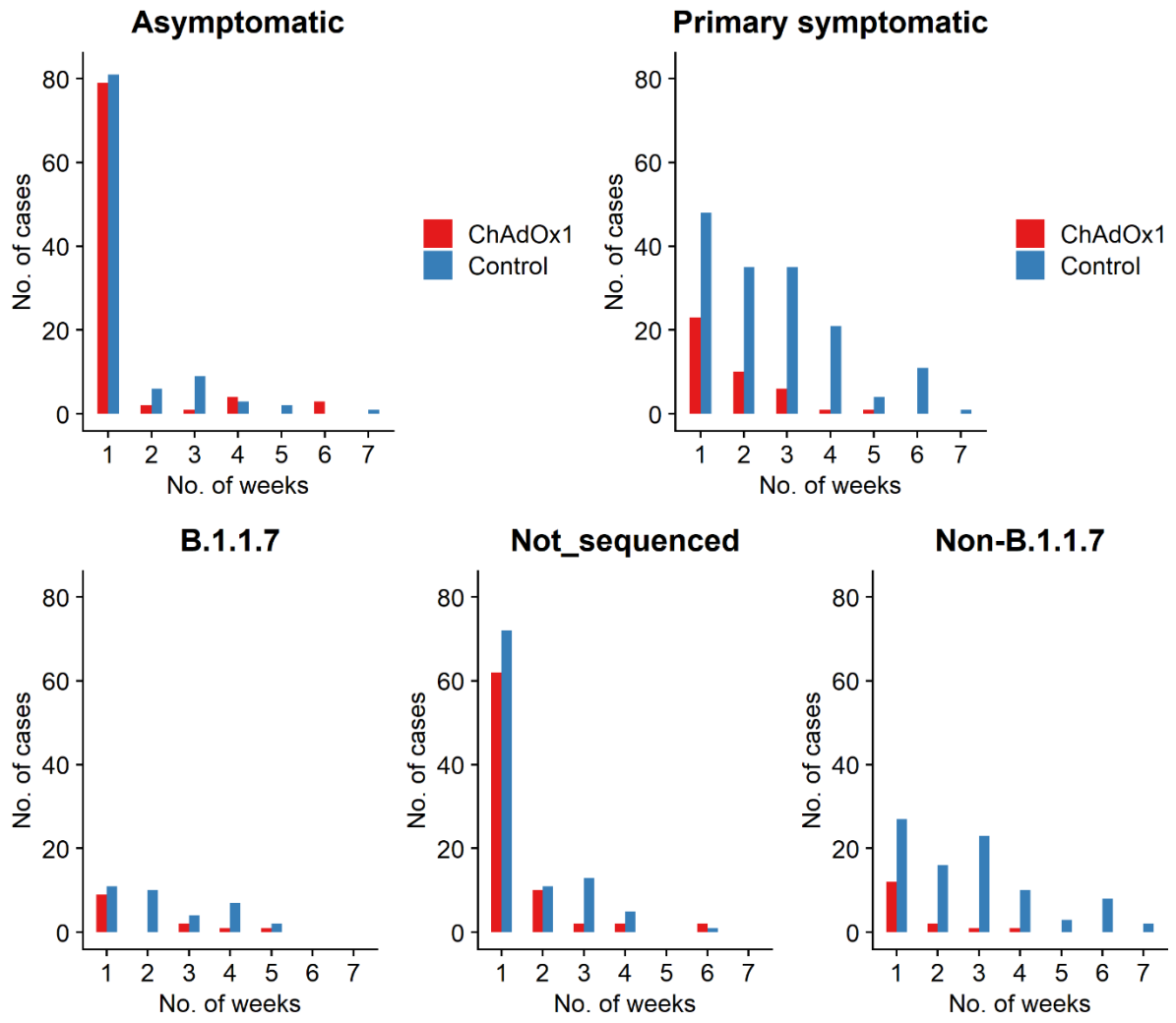


Ct values from positive PCR tests performed at Lighthouse laboratories using a ThermoFisher TaqPath 3-gene assay. Each data point represents one participant. For each participant the minimum of the Ct value for the N gene and ORF1ab gene was taken for each positive PCR swab, and the minimum across all swabs for the same person calculated as a proxy for maximum viral load. Low PCR Ct values are associated with higher viral load.

P values from Wilcoxon Rank Sum tests comparing ChAdOx1 nCoV-19 with control are: Overall p<0.0001, asymptomatic cases p=0.0040, primary symptomatic cases p=0.1534, B.1.1.7 variant p=0.0113, swabs not sequenced p=0.0164, non-B.1.1.7 variants p=0.0201.

Wilcoxon Rank Sum test: primary symptomatic cases vs asymptomatic cases: p<0.0001, B.1.1.7 cases vs non-B.1.1.7 p=0.0008.

Figure 5 Number of weeks from first NAAT positive swab to last positive swab returned†

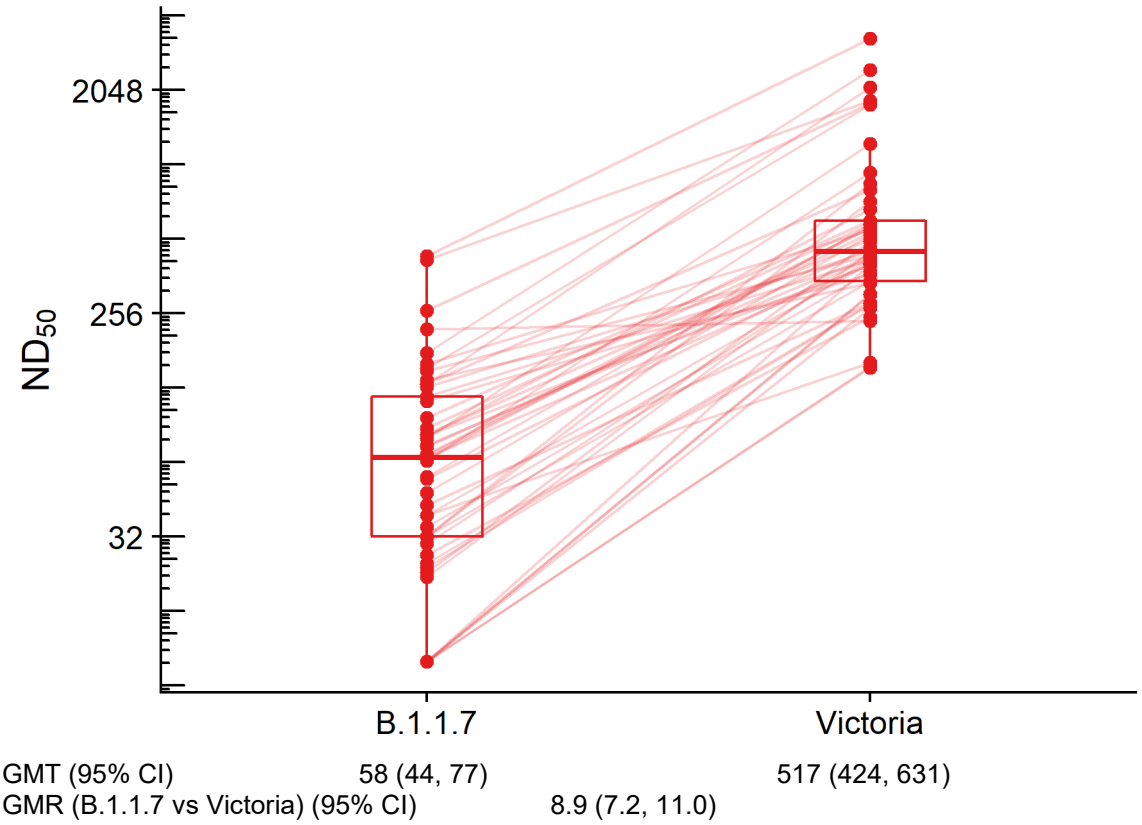


The number of weeks from the first NAAT positive swab recorded in the trial to the final NAAT positive swab recorded in the trial. We excluded results greater than 7 weeks from the plots as potential re-infections or false positives.

P values from Wilcoxon Rank Sum tests comparing ChAdOx1 nCoV-19 with control are: Overall p<0.0001, asymptomatic cases p=0.2551, primary symptomatic cases p=0.0062, B.1.1.7 variant p=0.1328, swabs not sequenced p=0.5176, non-B.1.1.7 variants p=0.0087.

Wilcoxon Rank Sum test: primary symptomatic cases vs asymptomatic cases: p<0.0001, B.1.1.7 cases vs non-B.1.1.7 p=0.5202.

Figure 6. Live virus microneutralisation antibody titres of sera against B.1.1.7 and a canonical non-B.1.1.7 (Victoria) strain



ND_{50}: titre at which 50% virus neutralisation is achieved. Lines connect samples from the same participant collected at the same trial timepoint

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