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Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: a test-negative, case-control study and a mechanistic study of post-vaccination immune responses

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Summary

Background SARS-CoV-2 variants of concern (VOCs) have threatened COVID-19 vaccine effectiveness. We aimed to assess the effectiveness of the ChAdOx1 nCoV-19 vaccine, predominantly against the delta (B.1.617.2) variant, in addition to the cellular immune response to vaccination.

Methods We did a test-negative, case-control study at two medical research centres in Faridabad, India. All individuals who had a positive RT-PCR test for SARS-CoV-2 infection between April 1, 2021, and May 31, 2021, were included as cases and individuals who had a negative RT-PCR test were included as controls after matching with cases on calendar week of RT-PCR test. The primary outcome was effectiveness of complete vaccination with the ChAdOx1 nCoV-19 vaccine against laboratory-confirmed SARS-CoV-2 infection. The secondary outcomes were effectiveness of a single dose against SARS-CoV-2 infection and effectiveness of a single dose and complete vaccination against moderate-to-severe disease among infected individuals. Additionally, we tested in-vitro live-virus neutralisation and T-cell immune responses to the spike protein of the wild-type SARS-CoV-2 and VOCs among healthy (anti-nucleocapsid antibody negative) recipients of the ChAdOx1 nCoV-19 vaccine.

Findings Of 2379 cases of confirmed SARS-CoV-2 infection, 85 (3·6%) were fully vaccinated compared with 168 (8·5%) of 1981 controls (adjusted OR [aOR] 0·37 [95% CI 0·28–0·48]), giving a vaccine effectiveness against SARS-CoV-2 infection of 63·1% (95% CI 51·5–72·1). 157 (6·4%) of 2451 of cases and individuals who had a negative RT-PCR test for SARS-CoV-2 infection between April 1, 2021, and May 31, 2021, were included as controls after matching with cases on calendar week of RT-PCR test. The primary outcome was effectiveness of complete vaccination with the ChAdOx1 nCoV-19 vaccine (aOR 0·54 [95% CI 0·42–0·68]), thus vaccine effectiveness of a single dose against SARS-CoV-2 infection was 46·2% (95% CI 31·6–57·7). One of 84 cases with moderate-to-severe COVID-19 had received a single dose compared with 153 of 2364 participants with mild disease (aOR 0·20 [95% CI 0·06–0·54]). Among 49 healthy, fully vaccinated individuals, neutralising antibody responses were lower against the alpha (B.1.1.7; geometric mean titre 244·7 [95% CI 151·8–394·4]), beta (B.1.351; 97·6 [61·2–155·8]), and delta (88·4 [61·2–127·8]) variants than against wild-type SARS-CoV-2 (599·4 [376·9–953·2]). However, the antigen-specific CD4 and CD8 T-cell responses were conserved against both the delta variant and wild-type SARS-CoV-2.

Interpretation The ChAdOx1 nCoV-19 vaccine remained effective against moderate-to-severe COVID-19, even during a surge that was dominated by the highly transmissible delta variant of SARS-CoV-2. Spike-specific T-cell responses were maintained against the delta variant. Such cellular immune protection might compensate for waning humoral immunity.

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Introduction

As of Oct 12, 2021, SARS-CoV-2 has affected more than 219 million people and caused more than 4 million deaths worldwide. The emergence of mutations in the virus has led to concerns regarding vaccine effectiveness. Some of the SARS-CoV-2 variants include alpha (B.1.1.7),
Evidence before this study
The delta (B.1.617.2) variant of SARS-CoV-2 has emerged as the predominant circulating strain contributing to the majority of infections worldwide. Evidence regarding immunological response and clinical effectiveness in individuals who have received the ChAdOx1 nCoV-19 vaccine is still emerging. We searched PubMed for articles published between January 1, 2021, and June 30, 2021, using the search terms “SARS-CoV-2”, “COVID-19”, “vaccine”, “ChAdOx1 nCoV-19”, and “immune response” alone or in combination. Our search yielded 147 articles about vaccine effectiveness and 56 about immune response. We identified five vaccine efficacy or effectiveness studies and ten articles on immune response to vaccines that were relevant to our study. Preliminary reports suggest that the delta variant is less susceptible than wild-type SARS-CoV-2 to in-vitro neutralisation by antibodies from recipients of two doses of the ChAdOx1 nCoV-19 vaccine. Surveillance data from the UK suggested that two doses of ChAdOx1 nCoV-19 vaccine might have a reduced effectiveness against infection, but comparable effectiveness against hospitalisation with the delta variant compared with wild-type SARS-CoV-2.

Added value of this study
This test-negative, case-control study showed that two doses of ChAdOx1 nCoV-19 vaccine provided 63.1% (95% CI 51.5–72.1) protection against infection attributed predominantly to the SARS-CoV-2 delta variant during the surge in infections observed in India between April and May, 2021.

Methods
Study design and participants
We did a test-negative, case-control study to assess vaccine effectiveness among individuals who attended Employee State Insurance Corporation Medical College (ESICMC) Hospital (Faridabad, India) or Translational Health Science and Technology Institute (Faridabad, India) for RT-PCR testing for suspected SARS-CoV-2 infection between April 1 and May 31, 2021.10 These two centres are the largest COVID-19 testing centres in Faridabad, contributing to 398,828 (91%) of 439,571 tests for all tests done in Faridabad.

All individuals who had a positive RT-PCR test for SARS-CoV-2 infection were included as cases. Controls were selected randomly using a computer programme from individuals who tested negative on RT-PCR and were matched on the basis of calendar week of test receipt during the study period.

For the mechanistic study, we enrolled 59 healthy individuals vaccinated at ESICMC Hospital who had received full ChAdOx1 nCoV-19 vaccination (appendix
Articles

The study was approved by the institutional ethics committees of ESICMC Hospital and the Translational Health Science and Technology Institute. Written informed consent was obtained from participants who contributed biospecimens, and verbal consent was obtained for the information collected for the vaccine effectiveness objective.

Data collection
Vaccination data, including the name of the vaccine, number of doses received, dates, and place of administration, and clinical manifestations of COVID-19 were obtained from cases and controls through a telephone questionnaire done by trained research staff. Quality control measures, methodological considerations for assessment of COVID-19 vaccination status, bias control, and confounding adjustments are described in the appendix (pp 2–5). Complete vaccination was defined as having the second dose of the vaccine at least 14 days previously. Single-dose vaccination was defined as having had the first dose of the vaccine at least 21 days previously but not having had the second dose. Unvaccinated individuals were those who had not received a single dose of vaccine and were included as the control group to estimate vaccine effectiveness for all analyses. Moderate-to-severe COVID-19 was defined if a patient reported at least one of the following: the need for oxygen supplementation, admission to intensive care, mechanical ventilation, or death.

Mechanistic study procedures
For the mechanistic study, blood samples were collected and processed for plasma and peripheral blood mononuclear cells (PBMCs; appendix p 7). To measure IgG antibodies, a recombinant spike protein RBD ELISA was done as described previously but with minor modifications, and antibody levels were calibrated against the WHO reference reagent (appendix p 6). Virus neutralisation assay titres were estimated as described previously. Briefly, plasma samples were serially diluted from 1/20 to 1/640 and incubated with one of four SARS-CoV-2 isolates (appendix p 5). 50% neutralisation values were calculated with four-parameter logistic regression using GraphPad Prism software (version 7.0e).

We expressed and purified recombinant RBD protein representing wild-type SARS-CoV-2 sequences, which were cloned in pCDN3.1 expression vector with CD5 secretory sequences. The RBD construct representing the VOCs was generated by introducing desired mutations one by one by site-directed mutagenesis, including Glu484Gln, Leu452Arg, Asn501Tyr, Lys417Asn, Glu484Lys, and Asn501Tyr, which are characteristic mutations in the alpha, beta, kappa, and delta VOCs (appendix pp 6, 7); the mutant RBD protein was then expressed in Expi293 cells (Thermo Fisher Scientific, Waltham, MA, USA).

CD4 and CD8 T-cell responses to stimulation with whole-spike peptide pools of wild-type and delta SARS-CoV-2 were tested with a cytokine bead array in culture supernatant of activated PBMCs, an activation induced marker assay, and an intracellular cytokine assay. To stimulate T cells, PBMCs were incubated with pools of 157 and 158 synthetic peptides (15-mer peptide pools overlapping by 11 amino acids) spanning the entire spike protein (PepMix; catalogue numbers PM-WCPV-S-1 and PM-SARS2-SMUT06-1; JPT Peptide Technologies, Berlin, Germany). To study the T-cell responses to mutant regions of the delta variant, we stimulated PBMCs with the commercially available PepTivator Prot-S B.6.1.7.2 mutant pool (Miltenyi Biotec, North Rhine-Westphalia, Germany). The mutant pool selectively covers the ten mutated regions in the spike protein of the delta variant with 32 15-mer peptides that include Thr19Arg, Gly142Asp, Glu156Gly, Phe157del, Arg158del, Leu452Arg, Thr478Lys, Asp614Gly, Pro681Arg, and Asp950Asn. A respective wild-type reference pool (Miltenyi Biotec) consisting of the 32 homologous peptides of wild-type SARS-CoV-2 was used as a control.

Antigen-specific CD4 and CD8 T-cell responses were determined by the production of the cytokines interferon-γ (IFNγ), interleukin-2 (IL-2), and tumour necrosis factor α (TNFα), and the effector molecules granzyme B and perforin expression. For cytokine production, 1×10⁶ cells per well were stimulated with 2 µg/mL peptide pool (PepMix) for 48 h and the culture supernatant was used to analyse the secretion of IFNγ, IL-2, and TNFα (appendix p 7). A similar number of PBMCs were seeded with dimethyl sulfoxide alone (unstimulated) as a negative control and the T-cell immune response was calculated by subtracting the readings of unstimulated PBMCs from the stimulated PBMCs. In all T-cell assays, phytohaemagglutinin 5 µg/mL was used as a positive control. Any sample with a low phytohaemagglutinin signal was removed for quality control.

To perform intracellular staining, 1 million cells per well were stimulated with 2 µg/mL peptide pool (PepMix) for 18–22 h and with monensin (Golgi Stop, BD Biosciences, Franklin Lakes, NJ, USA) for the final 6 h. Intracellular expression of IFNγ, IL-2, and TNFα in CD4 T cells and IFNγ, granzyme B, and perforin in CD8 T cells was tested in response to spike peptides pools of wild-type and delta variant SARS-CoV-2. The cells were stained for extracellular and intracellular markers and analysed using flow cytometry (appendix pp 7, 8). IFNγ-linked enzyme linked immunospot (ELISpot) was done to determine the frequency of IFNγ-secreting cells in response to wild-type and mutant peptide pools specific to delta variants (appendix p 9).
We did an activation-induced marker assay to gain a broader understanding of the total antigen-specific T-cell response. For the activation-induced marker assay, PBMCs were assessed as described previously (appendix pp 7, 8). Activation of both CD4 and CD8 T cells was measured by determining the surface expression of OX40 (TNFSF4) and CD137 (TNFRSF9) on CD4 T cells and CD69 and CD137 on CD8 T cells in response to stimulation with spike peptides pools of wild-type or delta SARS-CoV-2. To understand the RBD specific T-cell response, PBMCs were stimulated with wild-type and mutant RBD proteins as described previously. Response after 72 h of incubation was evaluated by IFNγ secretion in the culture supernatant (appendix p 8).

Sequencing libraries were prepared from the archived SARS-CoV-2 RNA samples using the amplicon-based COVIDSeq test kit (Illumina, San Diego, CA, USA). All synthesised libraries were sequenced on the NovaSeq 6000 platform with a read length of $2 \times 100$ bp (appendix p 9). Lineages were assigned using pangolin (version 3.0.5, pangoLEARN 2021-06-05).

Outcomes

Our primary outcome was real-world vaccine effectiveness of two doses of the ChAdOx1 nCoV-19 vaccine against laboratory confirmed SARS-CoV-2 infection. The secondary outcomes were vaccine effectiveness of a single dose of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection and vaccine effectiveness of a single dose and complete vaccination against moderate-to-severe disease among individuals infected with SARS-CoV-2. Additional outcomes for the mechanistic study were live-virus neutralisation and T-cell immune responses against VOCs among ChAdOx1 nCoV-19 vaccine recipients.

Statistical analysis

To detect a vaccine effectiveness of 60% for complete vaccination with ChAdOx1 against infection with 10% precision, and assuming that vaccine coverage among the controls was 10% (based on vaccination rates at the time of writing), we estimated that we needed a minimum of 4474 participants, with 2237 participants in each group, using the WHO vaccine effectiveness sample size tool (appendix p 2).

Data are presented as mean (SD) or median (IQR), as appropriate. The vaccine effectiveness of complete vaccination was estimated by comparison with unvaccinated individuals after exclusion of those who received a single dose and similarly, for the estimation of vaccine effectiveness for single dose vaccination, we excluded individuals with complete vaccination. Adjusted odds ratios (aORs) with 95% CIs were estimated using a multivariable logistic regression model, which included the following confounders decided a priori: age, sex, and risk of exposure (appendix p 4) as independent variables in addition to vaccination status. The final vaccine effectiveness estimate was calculated as vaccine effectiveness = $(1-aOR) \times 100\%$. Among individuals infected with SARS-CoV-2, the vaccine effectiveness of a single dose and complete vaccination for the prevention of moderate-to-severe COVID-19 was ascertained using individuals with mild COVID-19 as controls. To compare the live-virus neutralisation between different VOCs, the geometric mean titre for each variant was calculated and analysis of variance was done with the log-transformed titre values, using wild-type titres as the reference. We used Pearson’s correlation coefficient to assess the correlations between geometric mean titres of neutralising antibodies or quantitative IgG antibody levels and T-cell IFNγ and IL-2 production (measured in culture supernatant). The pair-wise fold change in IFNγ response against each variant versus wild-type was calculated and compared using the Wilcoxon matched-pairs signed-rank test. All statistical analyses were done using R (version 4.0.4).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

| Cases (n=2766) | Controls (n=2377) |
|---------------|-------------------|
| Age, years    | 35 (28–45)        | 32 (26–42)        |
| Sex           |                   |                   |
| Male          | 1804 (65.2%)      | 1626 (68.4%)      |
| Female        | 962 (34.8%)       | 751 (31.6%)       |
| High risk of COVID-19 exposure at workplace | 56 (2.0%) | 60 (2.5%) |
| Duration between the two vaccine doses among vaccinated participants, days | 33 (29–50; n=109) | 31 (28–45; n=202) |
| Mild COVID-19 symptoms | 2679 (96.5%) | NA               |
| Oxygen supplementation | 89 (3.2%) | NA               |
| Admission to the intensive care unit | 26 (0.9%) | NA               |
| Ventilatory support | 7 (0.3%) | NA               |
| Death         | 16 (0.6%)         | NA               |

Data are median (IQR) or n (%). NA=not applicable.

Table 1: Baseline characteristics of the participants included in vaccine effectiveness analyses
Figure 1: Study flow diagram
Neutralisation titres estimated by focus reduction neutralisation test are plotted in log-scale on the y-axis. The dots represent neutralisation titres of individual participants (n=49). The solid black line with error bars indicate geometric mean titres and 95% CIs. The sample numbers, geometric mean titre values, and fold change in titres between the variants of concern are shown in the appendix (p 12).

**Figure 2:** Titres of neutralising antibodies targeting wild-type SARS-CoV-2 and variants in plasma from ChAdOx1 nCoV-19 vaccine recipients

Neutralisation titres estimated by focus reduction neutralisation test are plotted in log-scale on the y-axis. The dots represent neutralisation titres of individual participants (n=49). The solid black line with error bars indicate geometric mean titres and 95% CIs. The sample numbers, geometric mean titre values, and fold change in titres between the variants of concern are shown in the appendix (p 12).

**Results**

Between April 1, 2021, and May 31, 2021, 8850 individuals had an RT-PCR test at the two centres, of whom 7132 (80·6%) responded when invited to participate in the study (4036 [78·2%] of 5163 RT-PCR test-negative individuals [controls]; 3086 [83·7%] of 3687 RT-PCR test-positive individuals [cases]). 169 individuals did not consent to the interview, 194 reported testing positive for COVID-19 (95·4%) of 2021, thus 3695 controls and 2883 cases were eligible for inclusion. After matching cases and controls and excluding individuals who had a negative test recorded in the database but reported a positive test later (n=476) and those who had received COVID-19 vaccines other than ChAdOx1 nCoV-19 (n=276), 2766 cases and 2377 controls were included in the vaccine effectiveness analysis (appendix p 3). The demographic, vaccination, and COVID-19 clinical characteristics of included participants are shown in table 1. The median interval between vaccine doses was 33 days (IQR 29–50) among cases and 31 days (28–45) among controls.

To estimate the effectiveness of two doses of ChAdOx1 nCoV-19 against SARS-CoV-2 infection, 2379 cases and 1981 controls were included in the analysis after exclusions (figure 1). 85 (3·6%) cases were fully vaccinated compared with 168 (8·5%) controls (aOR 0·37 [95% CI 0·28–0·48]), giving a vaccine effectiveness against SARS-CoV-2 infection of 63·1% (95% CI 51·5–72·1). Among the 84 cases of moderate-to-severe COVID-19, only one (1·2%) was completely vaccinated compared with 84 (3·7%) of 2295 cases with mild COVID-19 (aOR 0·19 [95% CI 0·01–0·90], thus effectiveness of complete vaccination against moderate-to-severe COVID-19 was 81·5% (95% CI 9·9–99·0). Among 87 participants with moderate-to-severe COVID-19, four (4·6%) were vaccinated with a single dose compared with 153 (6·5%) of 2364 with mild disease. Thus, a single dose of ChAdOx1 nCoV-19 prevented moderate-to-severe COVID-19 with an effectiveness of 79·2% (95% CI 46·1–94·0).

The neutralisation ability was tested in plasma from 49 of 59 fully vaccinated healthy participants. Their clinical characteristics are provided in the appendix (p 11). Blood samples were collected a median of 61 days (IQR 52–79) after the second vaccine dose. The median plasma IgG RBD antibody level was 234·6 ELISA laboratory unit/mL (IQR 88·0–452·4). The geometric mean titre of neutralising antibodies was 599·4 (95% CI 376·9–953·2) against the wild-type virus. A strong correlation was identified between the geometric mean titre against the wild-type strain and the corresponding IgG antibody levels (r=0·96 [95% CI 0·92–0·97]; appendix p 10). Geometric mean titres of neutralising antibodies were significantly reduced against SARS-CoV-2 variants compared with the
wild-type strain: geometric mean titres were 244·7 (95% CI 151·8–394·4; p=0·036) for the alpha variant, 112·8 (72·7–175·0; p<0·0001) for the kappa variant, 97·6 (61·2–155·8; p<0·0001) for the beta variant, and 88·4 (61·2–127·8; p<0·0001) for the delta variant (figure 2; appendix p 12).

The cytokine bead array was done in 48 available samples from vaccinated individuals, of whom 47 responded. No significant differences were observed in IFNγ, IL-2, and TNFa production between samples stimulated with wild-type and delta spike-specific peptide pools (figure 3A–C, table 3). The intracellular cytokine assay showed that the spike peptide pools of both wild-type and delta SARS-CoV-2 similarly induced the expression of IFNγ, IL-2, and TNFa in CD4 T cells and IFNγ, granzyme B, and perforin in CD8 T cells (figure 3D–I, table 3). Total antigen-specific T-cell responses also showed that both wild-type and delta SAR-CoV-2 spike peptides pools effectively and comparably induced surface expression of activation induced markers on CD4 and CD8 T-cells (figure 3J, K, table 3).

To further assess a more specific effect of mutant regions of the delta variant on the T-cell response, IFNγ-linked ELISpot was done. The antigen-specific T-cell immune response was conserved against the delta variant compared with wild-type SARS-CoV-2 (n=24; figure 3l). Compared with unstimulated controls, a robust T-cell response was observed from stimulated cells; secretion of IFNγ was higher for 19 of 24 samples, and thus these samples were considered as responders (appendix p 9). No significant correlation was identified between geometric mean titres of neutralising antibodies and

Figure 3: T-cell immune responses against spike antigens of wild-type and delta variant SARS-CoV-2 in samples from vaccinated participants

IFNγ (A), IL-2 (B), and IFNγ (C) concentrations in culture supernatant of peripheral blood mononuclear cells stimulated with peptide pools of wild-type and delta variant spike protein for 48 h (n=48; 47 of 48 samples responded to stimulation). Intracellular cytokine staining for IFNγ (D), IL-2 (E), and TNFa (F) in CD4 cells, and granzyme B (G), IFNγ (H), and perforin (I) in CD8 cells stimulated with peptide pools of wild-type and delta variant spike protein for 18–20 h; graphs show the proportions of cells expressing these molecules (n=41). Activation-induced marker assay of CD4 T cells (j) and CD8 T cells (K) stimulated with peptide pools of wild-type and delta variant spike protein for 24 h; graphs show the proportions of cells expressing these activation markers (n=38). (L) Antigen-specific activation of T-cells by peptide pools exclusively covering the mutant regions of the delta variant spike protein compared with the homologous wild-type reference peptide pool (n=19; 19 of 24 samples responded to simulation; mean 63·78 SFCs/10⁶ PBMCs for wild-type, and 45·68 SFCs/10⁶ PBMCs for the delta variant). Each datapoint represents the readings from the peptide pool-stimulated wells for one study participant, after subtraction of the dimethyl sulfoxide-stimulated wells.

IFNγ=interferon γ. SFCs=spot forming cells. TNFα=tumour necrosis factor α.
Discussion

In the absence of an effective antiviral therapy, vaccination remains the only strategy to mitigate the ongoing SARS-CoV-2 pandemic. ChAdOx1 nCoV-19 is one of the most commonly used vaccines. Multiple VOCs have the potential to jeopardise the effectiveness of vaccines. In a previous study, the ChAdOx1 nCoV-19 vaccine was found to be 10·4% (95% CI –76·8 to 54·8) effective against laboratory-confirmed symptomatic COVID-19 with the beta variant in a secondary endpoint analysis.20 In this study, we report a real-world effectiveness of 63·1% for complete vaccination with the ChAdOx1 nCoV-19 vaccine against laboratory-confirmed SARS-CoV-2 infection during the recent surge of COVID-19 cases caused by the delta variant in India.21 Studies from England and Scotland have reported effectiveness of 60·0–67·0% for the vaccine against infection by the delta variant.22–23 The delta variant has been shown to be 97% more transmissible than wild-type SARS-CoV-2 and has emerged as the dominant VOC across the world.24 Breakthrough infections due to the delta variant have been reported after vaccination with mRNA vaccines.22–25

The strengths of our study are use of the WHO-recommended test-negative, case-control design, which balances risk profile, health-care seeking behaviour, and access to care among vaccinated and non-vaccinated people, and the comparability of the vaccine effectiveness estimates with those of randomised trials.26 We minimised the potential bias of prioritised group for vaccination, such as elderly people, by adjusting for age, sex, and risk of COVID-19 exposure. The overall vaccination coverage at the time of the study was low in the Indian population. This low coverage needs to be considered when interpreting our findings since it is known that as vaccine coverage improves, disease incidence at the population level decreases.27 In our study, in addition to the low vaccine coverage, the majority of affected patients had mild COVID-19 with few severe COVID-19 manifestations, which could potentially make the estimates of vaccine effectiveness against severe disease unstable, as evidenced by the wide 95% CIs. We considered severe COVID-19 as a secondary outcome that was intended to be hypothesis generating to aid future studies to evaluate this outcome with adequate power. Our study population included predominantly young men, with a few at high risk of exposure in the workplace. This pattern, although fairly representative of our target population, emphasises the need for vaccine effectiveness studies in different settings to improve the generalisability of our results.

Mutations in the RBD region of the spike protein might compromise binding with neutralising IgG antibodies and thus the reduced neutralising efficacy of vaccine to the delta variant observed in a previous study.28 We also found neutralisation was significantly reduced in response to VOCs, particularly against the delta variant. The mutated proteins have been shown to escape neutralisation by...
monoclonal antibodies that are in clinical use. Although neutralising antibodies are important to prevent virus entry into host cells, an important defence mechanism is the cellular immune response against the virus. We studied the CD4 and CD8 T-cell responses against the SARS-CoV-2 full spike protein using overlapping peptide pools and RBD protein. We found no significant differences with regard to T-cell immune responses against wild-type or the delta variant of SARS-CoV-2. These observations are consistent with a previously published report, which showed that the reduction in total IFNγ secretion in response to variant peptide pools from among individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine or Moderna mRNA-1273 vaccine was not significant, indicating sufficient T-cell response against VOCs. Although CD4 and CD8 T-cell responses are key to viral clearance, it has been reported that the CD4 T-cell immune response is more important for controlling SARS-CoV-2 infection than the CD8 T-cell immune response. Considering the importance of CD4 T-cell responses in SARS-CoV-2 infection and that the RBD is one of the most immunogenic regions of spike proteins, we used full-length RBD protein to restimulate antigen-specific T cells, since protein stimulation primarily captures the CD4 T-cell reactivity in vaccinated individuals. Although there was a poor correlation between neutralising antibody geometric mean titres and IFNγ T-cell response, a significant positive correlation was observed between the antibody response and the IL-2 production by PBMCs. These observations are consistent with previous observations in COVID-19 convalescent individuals, in whom a poor correlation was identified between the humoral immune response and the T-cell immune response. A previous study showed that a conserved immunodominant $S_{346–365}$ region in the RBD protein comprising nested HLA-DR-restricted and HLA-DP-restricted epitopes is important for CD4 T-cell responses. This region is unaffected by the mutations in VOCs. Another study showed that almost 93% of CD4 T-cell epitopes and 97% of CD8 T-cell epitopes are conserved in SARS-CoV-2 variants. Hence, the cell-mediated immune response might be largely conserved against the point mutations generated in emerging variants of SARS-CoV-2.

From a policy perspective, a distinction between symptomatic disease and severe disease is important. Although neutralising antibodies might prevent symptomatic disease, cellular immune responses might prevent severe disease. Our study has shown that complete vaccination protected against moderate-to-severe COVID-19 even when the delta variant was dominant. It has been argued that breakthrough infections should only be diagnosed if a vaccinated person develops lower respiratory tract involvement since the vaccines are not designed to provide nasopharyngeal mucosal immunity. Our findings support this viewpoint that cellular immune responses might salvage reduced neutralising ability and prevent severe disease among vaccinated people even though protection against infection is compromised.

In summary, two doses of ChAdOx1 nCoV-19 vaccine were 63·1% effective against SARS-CoV-2 infection, caused mostly by the delta variant, and prevented moderate-to-severe COVID-19 in 81·5% of cases. COVID-19 vaccination policies should encourage complete vaccination in addition to other epidemiological public health measures to overcome the threat posed by the delta variant and other emerging variants of SARS-CoV-2.

Contributors
PKG conceptualised and designed the study. SbH, RT, and NW designed the study for clinical objectives. AA, GM, Ana, NG, SbHatt, and SM designed the study for laboratory objectives. AA, AB, TV, AZ, and DR designed, performed, and analysed T-cell assays. RT, WW, DRM, PKM, JT, AKP, SbHatt, SM, AB, TV, AZ, DR, NAK, HS, SSI, RP, VS, Ana, CS, and SV conducted clinical and laboratory experiments. TS, SSA, PK, RK, JB, PKM, JT, AKP, and NG provided resources. BKD, RT, DRM, AA, GM, SrS, RP, and VS conducted data analyses. PKG, RT, AA, GM, SSA, and TS verified the data, compiled the results, and wrote the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
The de-identified dataset and related codes for analysis will be made available to researchers on request after publication. Requests for data should be addressed to the corresponding author and will need to be approved by the Department of Biotechnology, Government of India (New Delhi, India).

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