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Immunogenicity of single vaccination with BNT162b2 or ChAdOx1 nCoV-19 at 5–6 weeks post vaccine in participants aged 80 years or older: an exploratory analysis

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Summary

Background In several countries, extended interval COVID-19 vaccination regimens are now used to accelerate population coverage, but the relative immunogenicity of different vaccines in older people remains uncertain. In this study we aimed to assess the antibody and cellular responses of older people after a single dose of either the BNT162b2 vaccine (tozinameran; Pfizer–BioNTech) or ChAdOx1 nCoV-19 vaccine (Oxford University–AstraZeneca).

Methods Participants aged 80 years or older, who did not live in a residential or care home or require assisted living, and had received a single dose of either the BNT162b2 vaccine or ChAdOx1 nCoV-19 vaccine were eligible to participate. Participants were recruited through local primary care networks in the West Midlands, UK. Blood samples and dried blood spots were taken 5–6 weeks after vaccination to assess adaptive immune responses using Elecsys electrochemiluminescence immunoassay and cellular responses by ELISpot. Primary endpoints were percentage response and quantification of adaptive immunity.

Findings Between Dec 29, 2020, and Feb 28, 2021, 165 participants were recruited and included in the analysis. 76 participants had received BNT162b2 (median age 84 years, IQR 82–89; range 80–98) and 89 had received ChAdOx1 nCoV-19 (median age 84 years, 81–87; 80–99). Antibody responses against the spike protein were detectable in 69 (93%) of 74 BNT162b2 vaccine recipients and 77 (87%) of 89 ChAdOx1 nCoV-19 vaccine recipients. Median antibody titres were of 19·3 U/mL (7·4–79·4) in the BNT162b2 vaccine recipients and 19·6 U/mL (6·1–60·0) in the ChAdOx1 nCoV-19 vaccine recipients (p=0·41). Spike protein-specific T-cell responses were observed in nine (12%) of 73 BNT162b2 vaccine recipients and 27 (31%) of 88 ChAdOx1 nCoV-19 vaccine recipients, and median responses were three-times higher in ChAdOx1 nCoV-19 vaccine recipients (24 spots per 1×10^6 peripheral blood mononuclear cells) than BNT162b2 vaccine recipients (eight spots per 1×10^6 peripheral blood mononuclear cells; p<0·0001). Humoral and cellular immune responses against spike protein were correlated in both cohorts. Evidence of previous SARS-CoV-2 infection was seen in eight participants (n=5 BNT162b2 recipients and n=3 ChAdOx1 nCoV-19 recipients), and was associated with 691-times and four-times increase in humoral and cellular immune responses across the whole cohort.

Interpretation Single doses of either BNT162b2 or ChAdOx1 nCoV-19 in older people induces humoral immunity in most participants, and is markedly enhanced by previous infection. Cellular responses were weaker, but showed enhancement after the ChAdOx1 nCoV-19 vaccine at the 5–6 week timepoint.

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Introduction

Vaccines have shown high levels of effectiveness against COVID-19-related illness, hospitalisation, and death.[1,2] A range of vaccine approaches have been developed for delivery of the spike immunogen, including mRNA, adenovirus, and protein-adjuvant platforms.[3] Most vaccine regimens use a two-dose protocol with some variation in the time interval between vaccines. The BNT162b2 mRNA vaccine (tozinameran; Pfizer–BioNTech) is authorised for administration at a 3-week interval,[4] whereas the interval for the ChAdOx1 nCoV-19 adenovirus vaccine (Oxford University–AstraZeneca) is longer, with evidence that delayed boosting might increase efficacy.[5]

To accelerate population coverage with COVID-19 vaccines, some countries have elected to delay the timing of the second dose by 10–12 weeks. Real-world evidence now indicates that this protocol is highly effective, with over 80% relative protection against hospitalisation and death in people aged 70 years and older.[2]

The BNT162b2 and ChAdOx1 nCoV-19 vaccines both display high clinical efficacy, but little attention has been given to assessment of their relative immunogenicity after single-dose administration. Information on single-dose

Research in context

Evidence before this study

Extended interval COVID-19 vaccine regimens are now used widely in many countries. Real-world evidence suggests clinical efficacy, but little is known regarding the relative induction of immune responses from different vaccines. This knowledge is of particular importance in older people in whom immunosenescence might limit immune responses.

Added value of this study

Here we compare and contrast the immune response against spike protein after one dose of either the BNT162b2 vaccine or ChAdOx1 nCoV-19 vaccine in older people (aged 80–96 years) living in community settings. We show that the two vaccines are equivalent in their ability to induce antibody responses at 5–6 weeks after vaccination. However, the proportion of people who generate a spike-specific cellular response, and the magnitude of this response, are both higher after the ChAdOx1 nCoV-19 vaccine.

Implications of all the available evidence

Cellular immune responses at 5–6 weeks after a single COVID-19 vaccine are stronger in older people who receive the ChAdOx1 nCoV-19 vaccine. The potential significance of this in relation to clinical protection prior to the second vaccine is currently uncertain.

immunogenicity is particularly needed in relation to their use in older people, where the influence of immunosenescence might limit immune responses.[6] Furthermore, older people are under-represented in the vaccine registration studies, and for the majority of people aged 80 years or older who live independently, data on immunological responses to the COVID-19 vaccines are lacking.

The BNT162b2 and ChAdOx1 nCoV-19 vaccines both deliver full spike protein, with BNT162b2 including a di-proline inclusion to stabilise the pre-fusion spike protein.[7] However, the different delivery systems are likely to mediate markedly different forms of antigen presentation, which might be reflected in a different profile or magnitude of humoral or adaptive immune response.

We compared adaptive immune responses in a population of older people who had received a single dose of either the BNT162b2 or ChAdOx1 nCoV-19 vaccines.

Methods

Study design and participants

Participants aged 80 years or older, who had received either the BNT162b2 vaccine or ChAdOx1 nCoV-19 vaccine and who did not live in a residential or care home, or did not require assisted living and who were living independently, were eligible for inclusion in the study. Comorbidities were permitted. Participants were recruited through local primary care networks in the West Midlands, UK. Participants were sent invitation letters, and were asked to contact the research team if they wanted to participate. After initial contact with the study team, participants were given the participant information sheet and consented verbally over the phone. This was substantiated with written consent obtained at the first phlebotomy timepoint. Ethical approval was obtained from The North West Preston Research Ethics Committee with favourable outcome (number REC 20\NW\0240). The study was done under the Coronavirus Immunological Analysis Urgent Public Health research study, according to the Declaration of Helsinki and good clinical practice.

Procedures All participants had received a single vaccination of either BNT162b2 or ChAdOx1 nCoV-19 as part of the UK-wide national COVID-19 vaccination programme. A 50 mL blood sample and dried blood spot were taken at the same time, 5–6 weeks after the first vaccine, for antibody testing for SARS-CoV-2 responses and IFN-γ ELISPot for cellular studies. This timepoint was selected as an approximate midpoint between first and second vaccines with an extended interval vaccination schedule. Samples were used for antibody and cellular studies in this exploratory study.

Outcomes

IgG, IgA, and IgM antibodies specific to SARS-CoV-2 were detected using electrochemiluminescence assays on the automated Cobas e801 analysers (Roche Diagnostics, Mannheim, Germany). Calibration and quality control were done as recommended by the manufacturer. Anti-nucleocapsid protein antibodies were detected using the qualitative Elecsys Anti-SARS-CoV-2 ECLIA (Roche Diagnostics, Indianapolis, IN, USA; COV2, product code 09203079190), while anti-spike antibodies were detected using the quantitative Elecsys Anti-SARS-CoV-2 S ECLIA (Roche Diagnostics, Indianapolis, IN, USA; COV2 S, product code 09289275190). Anti-nucleocapsid results are expressed as cutoff index values, with a value of 1·0 or more considered positive for anti-nucleocapsid antibodies. Anti-spike protein values of 0·8 U/mL or more were considered positive for anti-spike antibodies, within the fully quantitative range of the assay (0·4–2500 U/mL). Samples of more than 2500 U/mL were diluted further (1:10, 1:100, and 1:1000) to within the quantitative range.

IgG antibodies specific for SARS-CoV-2 were detected using chemiluminescent microparticle immunoassays run on the Alinity i-series platform (Abbott, North Chicago, IL, USA). Calibration and quality control were done as recommended by the manufacturer. Antibodies

were detected using the Alinity SARS-CoV-2 IgG II Quant assay (Abbott; master lot number 25346FN00, kit insert number 06S61), with samples with a result of 50 U/mL or more considered positive for anti-spike antibodies within the fully quantitative range of the assay (21–40 000 U/mL). The Alinity platform was set up to report results between 0·00 U/mL and 40 000 U/mL.

Quantitative IgG antibody titres were measured against spike protein, nucleocapsid protein, and other antigens using the V-PLEX COVID-19 Respiratory Panel 2 (96-well, ten spot plate was coated with three SARS-CoV-2 antigens [spike, spike receptor-binding domain, spike N-terminal domain, and nucleocapsid]; category number K15372U, lot number Z0056764; Meso Scale Discovery [MSD], Rockville, MD, USA). Antigens were spotted at 200–400 µg/mL. Multiplex MSD Assays were done as per the manufacturer's instructions. To measure IgG antibodies, 96-well plates were blocked with MSD Blocker A for 30 min. After washing with buffer, the samples were diluted 1:500 in diluent. Reference standards and positive controls and diluted samples were added to the wells. After a 2 h incubation, plates were washed three times with wash buffer and detection antibody (SULFO-TAG Anti-Human IgG Antibody, 1/200; Meso Scale Diagnostics, Rockville, MD, USA) diluted in diluent 100 was added. After 1 h of incubation at room temperature, the plates were washed three times with wash buffer. MSD GOLD Read Buffer B was added and plates were read immediately using a MESO QuickPlex SQ 120 (Meso Scale Diagnostics, Rockville, MD, USA). Text files were then generated from the Methodical Mind software and then transferred to the DISCOVERY WORKBENCH software, version 4.0. Data were then converted to AU/mL, exported as csv files, and then adjusted for any sample dilution.

Cellular assays

Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples using T-Cell Xtend (Oxford Immunotec, Oxford, UK) and Ficoll. After quantification and dilution of recovered cells, 250 000 PBMCs were plated into each well of a T-SPOT Discovery SARS-CoV-2 kit (Oxford Immunotec). This test measures responses to overlapping peptides pools, covering protein sequences of four different SARS-CoV-2 antigens, without HLA restriction, and includes negative control and phytohaemagglutinin-stimulated cells as a positive control. Peptide sequences that showed high homology to endemic coronaviruses were removed from the sequences, but sequences that might have homology to SARS-CoV-1 were retained. Cells were incubated and IFN-γ-secreting T cells were counted. A cutoff of 24 or more spots per million cells on the S1 pool was defined as a positive result, in line with the T-SPOT Discovery SARS-CoV-2 kit (Oxford Immunotec, Oxford, UK).

	BNT162b2, n=76	ChAdOx1 nCoV-19, n=89
Sex		
Female	45 (59%)	53 (60%)
Male	31 (41%)	36 (40%)
Age at first vaccination, years	84 (82–89)	84 (81–87)
Time between first vaccination and sample, days	40	39

Data are n (%), median IQR, or mean.

Table: **Participant demographics**

Statistical analysis

Data were tested for normality using Kolmogorov-Smirnov analysis. For comparative analysis of antibody titres and cellular responses between the BNT162b2 or ChAdOx1 nCoV-19 vaccine cohorts, a Mann-Whitney *U* test was done. Spearman rank correlation was used for comparing assay platforms for titres and correlating T-cell responses. Antibody titres are also presented as the geometric mean with SEM for each method of antibody assessment (appendix). The index of multiple deprivation decile scores were derived from residential postcodes using guidance on the national statistics website for England. All analysis was done using Graphpad prism, version 9.1.0.

See **Online** for appendix

For **residential postcode data** see https://imd-by-postcode.opendatacommunities.org

Role of the funding source

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

Results

Between Dec 29, 2020, and Feb 28, 2021, 165 participants were recruited and included in the analysis. 76 participants had received BNT162b2 (median age 84 years, IQR 82–89; range 80–98) and 89 had received ChAdOx1 nCoV-19 (median age 84 years, 81–87; 80–99; table). Participant demographics showed no differences in age or gender. The multiple deprivation score indices were marginally different in participants who received ChAdOx1 nCoV-19 (7, IQR 3–9) compared with participants who received BNT162b2 (4, IQR 4–6). Spike protein-specific antibody responses were assessed using quantitative Roche spike protein-specific ELISA and positive responses were seen in 69 (93%) of 74 participants after the BNT162b2 vaccine, and 77 (87%) of 89 participants after the ChAdOx1 nCoV-19 vaccine (p=0·32). Corresponding median antibody measurements were 19·3 U/mL after the BNT162b2 vaccine and 19·6 U/mL after the ChAdOx1 nCoV-19 vaccine (p=0·41). Responses were also assessed using the quantitative Abbott spike-specific ELISA; no significant difference was observed, with 62 (84%) of 74 participants responding to BNT162b2 and 69 (78%) of 89 participants responding after ChAdOx1 nCoV-19 (p=0·70;

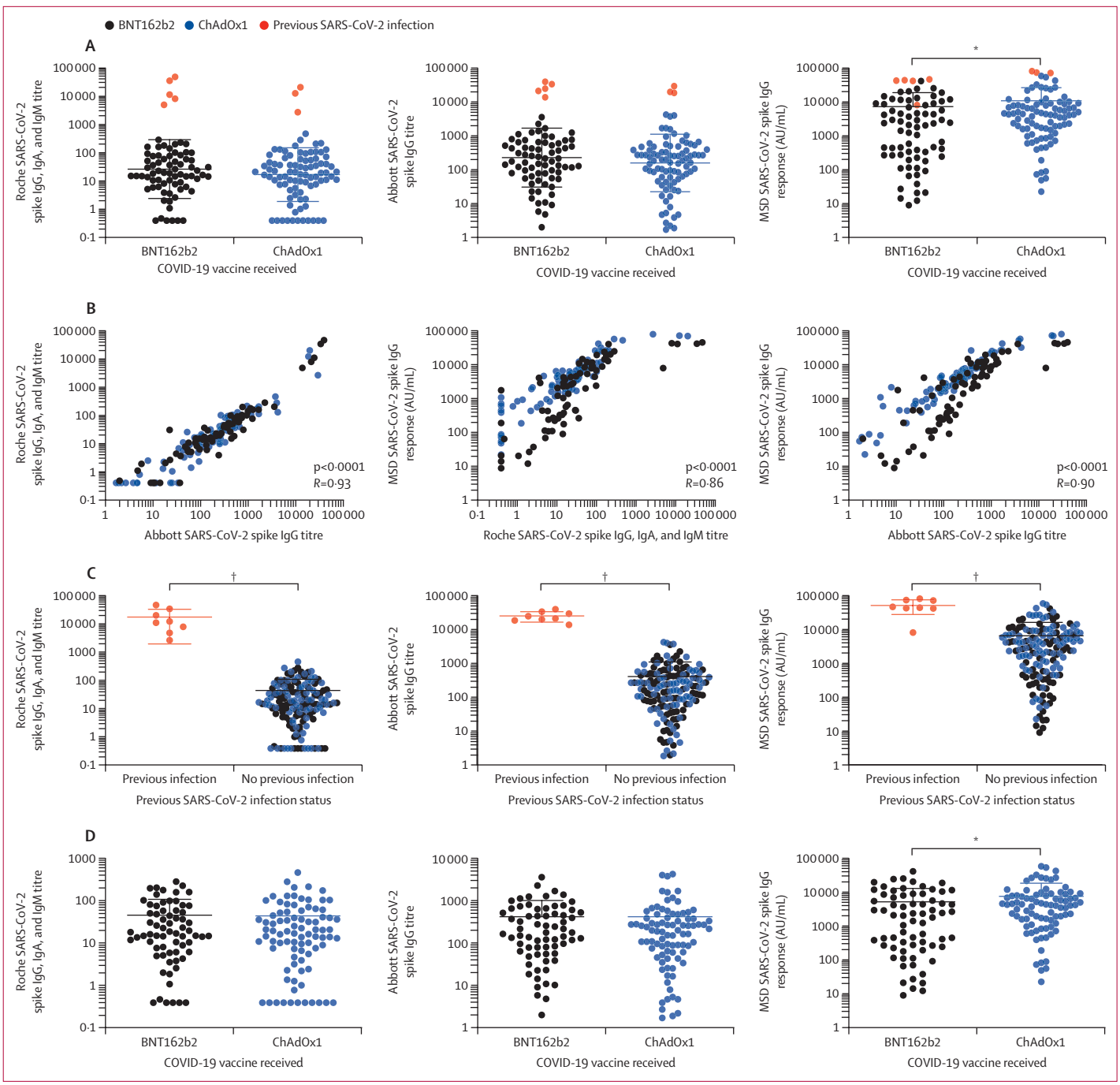

***Figure 1*: Spike protein-specific antibody responses after single vaccination with BNT162b2 or ChAdOx1 nCoV-19 in older people**

Spike protein-specific antibody responses (A) and correlation between spike protein-specific antibody responses (B) measured using Roche, Abbott, and MSD tests in participants after a single vaccination with BNT162b2 or ChAdOx1 nCoV-19 in the total cohort. Correlation was determined using Spearman's correlation test. (C) Comparison of spike-protein specific antibody responses in participants with previous SARS-CoV-2 infection or no previous infection after a single vaccination with BNT162b2 or ChAdOx1 nCoV-19. (D) Spike protein-specific antibody responses in participants without previous SARS-CoV-2 infection after single BNT162b2 or ChAdOx1 nCoV-19 vaccination. MSD=Meso Scale Discovery. *p<0·05. †p<0·0001.

figure 1; median 216 U/mL [IQR 75–680] in the BNT162b2 group *vs* 200 U/mL [60–478] in the ChAdOx1 nCoV-19 group; p=0·33).

Analyses were also done on the MSD platform to measure whole spike protein-specific or receptor-binding domain-specific responses. Using this platform, antibody responses were higher in participants who had received the ChAdOx1 nCoV-19 vaccine on both assays (p=0·04; figure 1). These data reveal some potential difference in the nature of the humoral response

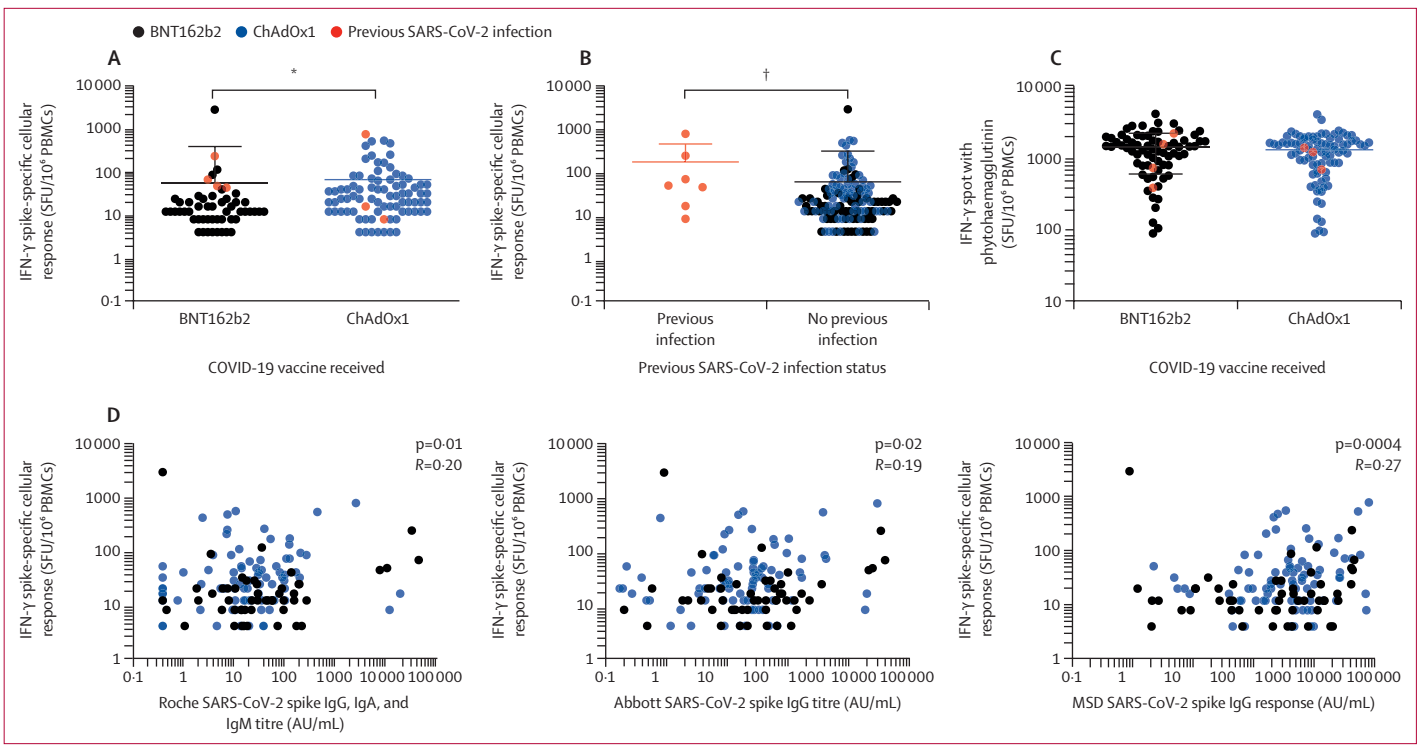

Figure 2: **Spike protein-specific cellular responses after single vaccination with BNT162b2 or ChAdOx1 nCoV-19 in older people**
(A) SARS-CoV-2 spike protein-specific cellular responses after single vaccination with BNT162b2 or ChAdOx1 nCoV-19. Assessment was by IFN-γ ELISpot. (B) Comparison of cellular responses in those with previous SARS-CoV-2 infection or no previous infection. (C) Positive control of IFN-γ ELISpot with phytohaemagglutinin stimulation. (D) Correlation between spike protein-specific cellular and humoral immune responses after single vaccination with BNT162b2 or ChAdOx1 nCoV-19, measured using Roche, Abbott, and MSD tests. PBMC=peripheral blood mononuclear cells. *p<0·0001. †p<0·05.

induced by the two vaccines, with associated variation on different assay systems, but strong correlations were observed between assays, and responses are overall similar after each vaccine (figure 1).

Eight participants showed evidence of previous SARS-CoV-2 infection on the basis of positive nucleocapsid protein-specific serology. Of these participants, five had received BNT162b2 and three had received ChAdOx1 nCoV-19. Spike protein-specific antibody titres by Roche ELISA were 691-times higher in these eight participants compared with participants without previous infection (n=11750 previous infection *vs* n=17 no previous infection; p<0·0001) and were also significantly higher in all other assay systems (figure 1).

To understand the efficacy of vaccination within infection-naive participants, we compared immune responses after exclusion of participants with previous SARS-CoV-2 infection. No difference was observed in spike protein-specific antibody titres by Roche (BNT162b2 n=17 *vs* ChAdOx1 nCoV-19 n=18; p=0·63) or Abbott platform (BNT162b2 n=178 *vs* ChAdOx1 nCoV-19 n=194; p=0·52), but a difference was observed using the MSD platform for spike protein-specific and receptor-binding domain-specific responses, with higher titres observed after the ChAdOx1 nCoV-19 vaccine (BNT162b2 p=0·01 *vs* ChAdOx1 nCoV-19 p=0·0004; figure 1).

We next assessed the induction of spike protein-specific T-cell responses after vaccination using IFN-γ ELISpot, which detects CD4-positive and CD8-positive T-cell responses. Cellular responses were detectable at 5 weeks after a single dose of BNT162b2 in nine (12·3%) of 73 participants and in 27 (30·7%) of 88 participants after a single dose of ChAdOx1 nCoV-19. Furthermore, the magnitude of cellular responses was three-times greater within the ChAdOx1 nCoV-19 subgroup at 24 spots per 1×10^6 PBMCs compared with eight spots per 1×10^6 PBMCs after BNT162b2 (p<0·0001), and this difference remained after exclusion of participants with previous SARS-CoV-2 infection (24 spots per 1×10^6 PBMCs *vs* eight spots per 1×10^6 PBMCs; p<0·0001). Participants with serological evidence of previous SARS-CoV-2 infection showed a four-times increase in cellular responses compared with participants with no previous infection (previous infection median 48 *vs* no previous infection median 12; p=0·002; figure 2).

We next assessed the relationship between spike protein-specific cellular and humoral responses and found cellular responses to be correlated positively with antibody titres from all four assay systems (figure 2).

Discussion

Extended dose COVID-19 vaccine protocols have been initiated in several countries, and have shown high levels of clinical protection after the first dose.[2] Here we assessed the immune responses after single COVID-19 vaccinations in a population of people aged 80–96 years, in whom vaccine responses against infections such as influenza are often suboptimal.[6,8] We recruited 165 participants of the appropriate age within the logistical timeframe offered by the vaccination programme and while under lockdown restrictions . Our results show reassuring levels of humoral immunity after one dose of BNT162b2 or ChAdOx1 nCoV-19, which is likely to correlate with protection against primary infection; however, the ChAdOx1 nCoV-19 adenovirus-based platform was associated with induction of a stronger cellular immune response than vaccination with the mRNA-based BNT162b2 vaccination.

Measurable spike protein-specific antibody responses were observed in more than 87% across all vaccine recipients. The median titre of spike protein-specific antibody was 19·3 U/mL, which was lower than that reported in younger individuals.[9–11] Antibody responses after one dose of either vaccine were similar, as measured using the Roche and Abbott assays; however, results were significantly higher after vaccination with ChAdOx1 nCoV-19 when measured using the MSD platform. The reasons for these results are unclear, but do not appear to be related to factors such as isotype assay.

We observed a 691-times increase in median antibody titre after vaccination in participants who had previous SARS-CoV-2 infection. A similar result was observed previously in people with a median age of 40 years who were given the BNT162b2 or elasomeran (CX-024414; Moderna) vaccines, but the relative increase was only 45 times.[12] In health-care workers, a more modest 6·5-times increase was observed after one vaccination with BNT162b2 in participants with previous SARS-CoV-2 infection.[10] This result indicates a 15-times further increase in infection-priming in older people,[12] and is a similar relative enhancement to that we observed in patients with immune suppression (unpublished data). It appears probable that natural infection markedly enhances the breadth and quality of spike protein-specific immune responses, and to overcome some of the negative influences of age on the vaccine-induced immune response. The mechanisms behind this finding will be necessary to investigate further, and could provide insight into the optimal nature and timing of booster vaccinations.

We noted a marked difference in the induction of spike protein-specific cellular responses, whereby the ChAdOx1 nCoV-19 vaccine resulted in a three-times higher median virus-specific T-cell response than BNT162b2. This vaccine platform has been shown previously to induce strong cellular immunity, which might be reflected in our observations.[13,14] The mechanisms that led to improved celluar response are not clear, but might relate to an adjuvant effect from the adenovirus vector. The Johnson & Johnson vaccine, which is also based on an adenoviral delivery system, is now licensed for single-dose administration, and has been shown to induce effective immune responses and strong clinical protection.[15] It is important to highlight that this comparison reflects only a single timepoint, and differences in the kinetics of humoral and cellular responses after the two vaccine platforms might differ.

In the present study, across the whole cohort, cellular responses were lower than has been reported for younger participants after single-dose vaccination, which might reflect the effect of immunosenescence within our cohort.[10] As such, any potential negative effect of ageing might be more noticeable in relation to cellular response than humoral immunity. At this stage, the importance of cellular immunity in relation to protection from infection is unclear for SARS-CoV-2. Influenza-specific cellular responses have been shown to limit the severity of infection, and this effect might also be the case for SARS-CoV-2 infection.[16] However, there is currently no evidence of differential control of severe clinical outcomes after a single vaccination with either BNT162b2 or ChAdOx1 nCoV-19. Cellular-specific immune responses might also be of value in supporting and maintaining humoral immunity over the long term, and as such it will be of interest to study this cohort over time.

In our cohort of older people, T-cell responses were measured on the standard assessment of IFN-γ secretion, but this does not preclude the presence of spike protein-specific T cells that make other inflammatory cytokines, and this possibility will be assessed going forward. The possible presence of other spike protein-specific T cells will be particularly important in this cohort, in whom the balance of inflammatory and anti-inflammatory cytokines associated with inflammaging can modulate responsiveness to vaccination and might be influenced by the type of vaccine platform and adjuvant used.

Our study is limited by the fact that it was exploratory, and therefore not randomised. An assessment was therefore made to consider potential selection bias. We are not aware of any known confounding demographic association between vaccine type and immune response. Potential confounding differences between the BNT162b2 and ChAdOx1 nCoV-19 cohorts include differences in comorbidities, lifestyle, and medication, but this information was not available for analysis. Participant demographics showed no differences in age or gender. Participants who received BNT162b2 were living in slightly more socioeconomically deprived areas. To the best of our knowledge, there has not been any study of COVID-19 vaccine-induced immune responses in relation to social deprivation index. It is possible that social deprivation index might affect vaccine-induced immune responses, but clinical protection after vaccination appears equally strong across the whole population.

The approved regimen for BNT162b2 vaccination is the delivery of two doses at 3 weeks apart, and the second vaccine strongly enhances humoral and cellular immunity.[10,17] As such, our findings relate only to assessment of vaccine efficacy in relation to an extended-interval second dose, where both vaccines have shown strong clinical efficacy. The immune correlates identified in our study should be studied futher in long-term assessment of clinical responses in this older age group.

Contributors

HP, RB, and PM designed the study. PM, HP, and JZ wrote the Article. HP, RB, and RM recruited participants. SH, JZ, CS, SF, GT, AR, and HP did the experiments. HP, JZ, PM, and DG verified and analysed the data. MA, AO, BH, and AH did the experiments. GA and KB designed the study. All authors had full access to the data and approved submission of this Article. PM had the final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The de-identified data used in this study can be shared after approval by the ethics authority and on request to the corresponding author.

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