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Assessing the effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID19 vaccination in prevention of hospitalisations in elderly and frail adults: a single centre test negative case-control study

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Abstract

Background

On 8th December 2020, deployment of the first SARS-CoV-2 vaccination authorised for UK use (mRNA vaccine BNT162b2) began, followed by adenoviral vector vaccine ChAdOx1nCoV-19 on 4th January 2021. Initially care home-residents and staff, frontline healthcare workers and adults ≥80y were targeted. However, few data exist regarding effectiveness of these vaccines in elderly frail people. Post-implementation evaluation to determine one dose effectiveness in reducing SARS-CoV-2 infection hospitalisations in elderly adults is urgent.

Methods

We undertook a prospective single-centre test-negative design case-control study of adults aged ≥80 years hospitalised in Bristol, UK, with COVID19 or other acute respiratory disease. We conducted logistic regression controlling for time (week), gender, index of multiple deprivations (IMD), and care residency status (CRS), and sensitivity analyses matched for time and gender using a conditional logistic model adjusting for IMD and CRS.

Findings

466 adults were eligible (144 cases, 322 controls). 18/135 cases (13.3%) with SARS-CoV-2 infection and 90/269 controls (33.5%) received one dose BNT162b2. The adjusted vaccine effectiveness was 71.4% (95% confidence interval [CI] 46.5-90.6). 9/36 cases (25%) with COVID19 infection and 53/90 controls (58·9%) received one dose ChAdOx1nCoV-19. The adjusted vaccine effectiveness was 80.4% (95% CI 36·4-94·5). When BNT162b2 effectiveness analysis was restricted to the period covered by ChAdOx1nCoV-19, the estimate was 79.3% (95% CI 47·0-92·5).

Interpretation

One dose of either BNT162b2 or ChAdOx1nCoV-19 resulted in substantial risk reductions of COVID19-related hospitalisation in elderly, frail patients with extensive co-morbid disease.

Funding

The AvonCAP study is an investigator-led project funded under a collaborative agreement by Pfizer.

Research in context

Evidence before this study

We searched PubMed and medRxiv for observational studies until 10th February 2021 using the terms "COVID19 vaccine effect"; "SARS-CoV-2" or "COVID-19"; "vaccine" and "effectiveness". A control study found one dose of BNT162b2 has an estimated effectiveness against symptomatic disease in ≥70-year-olds of 62% (95% confidence interval [CI] 43-77) at 14-21 days and 73% (95% CI 62-82) at 21-27d after first dose. A Public Health England authored paper using positive testing demonstrated a relative risk of hospitalisation of 0.57 (0.48-0.67) and 0.63 (0.41-0.97) more than 14 days after first dose in adults ≥80 years with BNT162b2 or ChAdOx1nCoV-19 respectively. A preprint reported one dose vaccine effectiveness against hospitalisation of 85% (95% CI 76 to 91%) and 94% (73-99) 28-34 days following first dose BNT162b2 and ChAdOx1nCoV-19 respectively, and in adults aged ≥ 80 years 81% (65-90) for the 2 vaccines analysed together. One preprint reported a 51% relative risk reduction against SARS-CoV-2 symptomatic infection 13-24 days after the first BNT162b2 vaccine dose, in a cohort of 503,875 individuals. The SIREN study in healthcare workers under 65 found one dose vaccine effectiveness of BNT162b2 of 70% against SARS-CoV-2 symptomatic infection.

Added value of this study

Currently limited real-world data exist on one dose effectiveness of BNT162b2 and ChAdOx1 nCoV-19 and limited data for ChAdOx1nCoV-19 effectiveness against COVID19 disease in elderly patients. This test-negative design case control study reports the effect of one dose of BNT162b2 and ChAdOx1nCoV-19 vaccines against hospitalisation in elderly, frail patients using symptom onset to determine vaccine effect, which increases accuracy when determining one dose vaccine effectiveness, addressing an urgent public health question. We excluded

patients with symptoms starting more than 10 days before admission, to reduce bias from false negative SARS-CoV-2 tests.

Implications of all the available evidence

This paper provides evidence that one dose of either BNT162b2 or ChAdOx1nCoV-19 vaccine, currently utilised in the UK vaccination programme, substantially reduces the risk of COVID19-related hospital admissions, in individuals ≥80 years old on 31st March 2021, frail and with extensive co-morbid disease.

Introduction

SARS-CoV-2 has resulted in a global pandemic with over 153954491 cases and 3221052 deaths as of 6th May 2021.[1] The authorisation of several vaccines has followed multiple international randomized controlled trials. Two vaccinations against SARS-CoV-2 were in use in the United Kingdom: an mRNA-based vaccine (BNT162b2) produced by Pfizer Inc and BioNTech SE; and, a replication-deficient simian adenovirus vector ChAdOx1nCoV19 from Oxford University and AstraZeneca. Both contain nucleic acid coding for the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2. Two doses BNT162b2 have 95% efficacy (95% credible interval 90-98) ≥7 days after second dose against symptomatic SARS-CoV-2 infection in participants without evidence of prior COVID19 infection.[2] Recently, Israeli researchers reported effectiveness of 73% (95% Confidence Interval [CI] 62-82) at 21-27 days after first dose against symptomatic disease in >70 year-olds.[3] Two doses ChAdOx1nCoV-19 have 70% efficacy ≥14 days after second dose against symptomatic SARS-CoV-2 infection in seronegative participants [4] with some evidence of increasing protection as dose interval increases.[5] Evidence shows neutralising antibody detectable 28 days following a single ChAdOx1nCoV-19 dose in adults ≥70 years. [6] Data from Public Health England (PHE) demonstrate a relative risk of hospitalisation of 0.57 (0.48-0.67) and 0.63 (0.41-0.97) more than 14 days after first dose in adults ≥80 years with BNT162b2 or ChAdOx1nCoV-19 respectively, using date of testing positive and hospitalisation.[7]

The UK Medicines & Healthcare Products Regulatory Agency (MHRA) granted first use authorisation worldwide for BNT162b2.[8] The UK national BNT162b2 vaccination programme commenced on 8th December 2020. Authorisation for ChAdOx1nCoV-19 followed on 30th December 2020, and first administration of ChAdOx1nCoV-19 on 4th January 2021.

The Joint Committee on Vaccination and Immunisation (JCVI) advised targeting vaccines towards those at highest risk: care home residents and their carers; patients aged ≥80 years; and, frontline health and social care workers.[9] However, several other European countries have deferred implementation of ChAdOx1nCoV-19 in adults aged over either 55 or 65 years for lack of efficacy or effectiveness evidence in those age groups, despite high infection and hospitalisation incidences.

Following the introduction of both vaccines, the JCVI advised delaying second dose administration, enabling first vaccine dose prioritisation to increase short-term public health impact and reduce preventable deaths. Whilst maintaining support for a two-dosing regimen, the JCVI recommended extending the maximum interval between doses from three (BNT162b2) and four weeks (ChAdOx1nCoV19) to 12 weeks for both vaccinations.[10] In the context of these policies, we undertook a test-negative case control study to assess the effectiveness of a single BNT162b2 and ChAdOx1nCoV19 vaccine dose against SARS-CoV-2 related hospitalisations in adults in Bristol, UK.

Methods

Study Design and Conduct

We conducted a test-negative case-control study [11,12] of consecutive adults admitted to North Bristol or University Hospitals Bristol and Weston NHS Trusts with signs and symptoms of respiratory disease between 18th December 2020, 10 days after first BNT162b2 administration, and 26th February 2021 inclusive. Enrolment commenced at this time point as the Kaplan-Meier graph in the Phase 3 BNT162b2 study showed divergence between controls and vaccinees from 10 days. [2] Patients with signs and symptoms of respiratory infection and who would be ≥80 years on 31st March 2021, the age group initially targeted for vaccination, were included in this analysis. A clinician identified eligible cases and controls from the medical admission list. Clinical data were collected from electronic and paper patient records and recorded on an electronic clinical record form using REDCap.[13] Data collection methods were identical for cases and controls. To avoid observer bias, collection of all data was undertaken by individuals not involved in data analysis and blinded to results.

Vaccination records for each study patient were obtained from linked hospital and GP records, including vaccinations delivered at vaccination hubs, vaccination brand and date of administration. Vaccination data were collected by individuals blinded to participants' SARS-CoV-2 test results.

Case definition

All adults admitted to participating hospitals were screened for signs and symptoms of respiratory disease. These included: documented fever (≥38°C) or hypothermia (<35.5°C);

cough; increased sputum volume/discolouration; pleurisy; dyspnoea; tachypnoea; examination findings compatible with acute lower respiratory tract disease (e.g., crepitations); and/or radiological changes suggestive of acute respiratory tract disease. Only patients with ≥two of these signs, or a confirmed clinical/radiological diagnosis of acute lower respiratory tract disease were included. Cases were defined as having symptomatic respiratory disease and a positive admission result for SARS-CoV-2, using Hologic Panther TMA assay conducted by PHE diagnostic laboratories[14]. Controls had to have respiratory disease and negative SARS-CoV-2 result.

Exposure definition

We studied the effectiveness of the first dose of BNT162b2 (Pfizer) vaccine and ChAdOx1nCoV-19 (Oxford-AstraZeneca) vaccine. Individuals were defined as exposed if they received a single dose of either vaccine between 8th December 2020 (Pfizer) or 4th January 2021 (Oxford-AstraZeneca) and 12th February 2021, with recruitment censored at 26th February 2021 – the latest event date. Unvaccinated/unexposed individuals in the analyses had received neither vaccine.

Outcomes and exclusions

We assessed vaccine effectiveness (VE) of first doses against hospital admissions with respiratory infection. Patients developing symptoms before vaccine-receipt or vaccine-receipt after admission were excluded, as were those with symptoms that started more than 10 days prior to admission to avoid including patients with potentially false negative admission SARS-CoV-2 tests. To avoid bias due to nosocomial infection, readmissions were excluded. VE of first dose was assessed ≥14 days after receipt of first dose. Those developing symptoms within

14 days of receipt of first vaccine dose were excluded from primary analysis but assessed in a separate bias detection analysis (negative control).

Statistical Analysis

Prior to study initiation, a sample size calculation was completed to ensure feasibility.[15,16] Whilst very sensitive to vaccine uptake in controls, this predicted that with 80% power and a 2-sided α of 0·05; at 80% receipt of first dose in controls an odds ratio (OR) of vaccination of 0·3 could be detected from at least 53 cases.

VE was defined as 1-OR of receipt of one dose. The proportion of cases who received one dose was compared to that in controls using adjusted and unadjusted regression analyses. Due to the evolving nature of both the COVID19 epidemic and rollout of the vaccine programme, we recognise that changes over time could introduce biases and confound results. To mitigate this, we performed unmatched logistic regression analyses adjusting for week of symptom onset as well as gender, care home residency and Decile rank of Index of Multiple Deprivations (IMD) and an additional analysis matching cases and test-negative controls by gender and week of symptom onset and adjusted for deprivation and care home-residency using conditional logistic regression.[17] Finally, to explore the possible impact of instabilities during the first weeks of the programme, we analysed the apparent effectiveness of BNT162b2 during the period in early 2021 when ChAdOx1nCoV-19 was also used. To assess likely levels of residual bias, we performed a negative control analysis - calculating apparent effectiveness of one dose of vaccination during the period up to 14 days after administration, when no protection was expected. Analyses for each vaccine were carried out separately.

Proportions were compared using Fisher exact tests and parametric data using t-tests. Statistical analyses were performed with R, version 4.0.2. Missing data were minimal with 26 patients for whom vaccine status could not be determined (Figure 1), and no imputation was performed. Statistical significance was defined using 2-sided significance level $\alpha = 0{\cdot}05$.

Ethics and permissions

The study was approved by Health Research Authority Research Ethics Committee (East of England, Essex), REC 20/EE/0157, including data collection under Section 251 of the 2006 NHS Act authorised by the Confidentiality Advisory Group.

Role of the funding source

The study sponsor collaborated in the design of the study and commented on the drafted manuscript. The sponsor had no role in data collection, data analysis, data interpretation, nor writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

By the 12th February 2021, National Immunisation Management Service data showed 95·0% (44844/ 47355) adults aged ≥80 years and resident in Bristol, UK had received a first dose of a COVID19 vaccine.[18] 6673 adults were hospitalised in Bristol over the study period. 2741 had signs or symptoms of respiratory disease. Of the hospitalized adults with respiratory disease, 803 (29%) were ≥80 years, 466 were eligible for the study. Of these 144 (31%) tested positive for SARS-CoV-2. The designation and exclusion of cases and controls is shown in Figure 1 and 2. The period of observation from vaccination to data cut on 26th February 2021 for this analysis ranged between 34 and 80 days for BNT162b2 and between 19 and 64 days for ChAdOx1nCoV-19.

Among BNT162b2 analysis cases with confirmed COVID19, median age was 87·3 (IQR 83·3 - 90·7) years, 66 (49%) were male, and 30 (22%) were care home residents. 115 (85%) were classified frail on the Rockwood frailty score, and the median Charlson Co-morbidity Index (CCI) was 6·0 (5·0-7·0) with associated 10-year survival under 30%. [19] Characteristics of cases and controls used in this analysis are listed in Table 1.

108 individuals received a single dose of BNT162b2 vaccination more than 14 days before symptom onset. The primary outcome for one dose of BNT162b2 is shown in Table 2, and care home status did not substantially alter the headline result. 18 of the 135 cases (13.3%) with SARS-CoV-2 infection and 90 of 269 controls (33.5%) received one dose BTN162b2 (difference, -20.2% giving an unadjusted effectiveness of 69.4% (95% CI 47.7-82.9) and an adjusted effectiveness of 71.4% (95% CI 43.1-86.2). Matched conditional sensitivity analysis generated a slightly lower estimate with wider confidence intervals which crossed zero, owing

to imperfect matching (see table 2). Imperfect matching occurred if at each time point one group is already entirely matched and there were consequently left over cases/controls. The apparent effectiveness up to 14 days was close to zero (OR 0.935) suggesting limited bias was present in the cohort.

Among the ChAdOx1nCoV-19 analysis cases with confirmed COVID19, median age was 88·3 (84·2 - 90·6), 17 (47 %) were male, and 12 (33 %) were care home residents. 31 (86%) were classified as frail on the Rockwood score, and the median CCI was 5·0 (IQR 5-6.2). The cases and controls used in the analysis are characterised in Table 1.

62 (14%) individuals received a single dose of ChAdOx1nCoV-19 vaccination more than 14 days before symptom onset. The primary outcome for one dose ChAdOx1nCoV-19 is shown in Table 2. Again care home status did not substantially alter the result. 9 of the 36 cases (25%) with SARS-CoV-2 infection and 53 of 90 controls (58·9%) received one dose ChAdOx1nCoV-19 (difference, -33.9% giving unadjusted effectiveness of 76.7 (95% CI 46.5-90.6) and adjusted effectiveness of 80.4% (36.4-94.5). Matched conditional sensitivity analysis again generated a slightly lower estimate with wider confidence intervals which crossed zero. Again, apparent effectiveness up to 14 days was close to zero (OR 1.126) and, since this is the expected biological reality, this provides some support that there was limited bias present in the cohort..

Comparison of subjects receiving each vaccine is shown in Table 3. Due to vaccine delivery logistics in Bristol, compared to those vaccinated with ChAdOx1nCoV-19, recipients of BNT162b2 were significantly less likely to be a care-home resident and be classified frail. However, when analysis of one dose BNT162b2 effectiveness was restricted to the period

covered by the ChAdOx1nCoV-19 analysis after the end of 2020, the observed adjusted estimate was 79.3% (95% CI 47.0-92.5) (*P*=0.0014).

Discussion

As rollout of available COVID19 vaccines commences, there is an urgent need for real-world effectiveness data, particularly relating to severe disease in persons ≥80 years: a high-risk group and a primary target for the UK vaccination programme. Furthermore, few persons ≥80 years were enrolled in vaccine randomized control trials. All observational studies are subject to bias and never more so than in the context of current rapid changes in disease epidemiology and vaccine deployment strategy and operationalisation. By undertaking a comprehensive prospective systematic surveillance study in two large hospitals in one city, we were able to collect a much more detailed and accurate dataset than can be obtained from routine coding and admission databases. Although this work is ongoing and will deliver more granularity and precision over time, initial results are of immediate relevance to formulation of and adjustments to current vaccination strategies in different countries using these vaccines.

The observed VE of one dose of BNT162b2 against hospital admissions presented in this study estimates one dose effectiveness in adults ≥80 years on 31st March 2021 with extensive co-morbid disease. The BNT162b2 phase 3 randomised controlled trial enrolled few adults ≥80 years and evaluated efficacy of two doses of BNT162b2 against symptomatic COVID19; although the trial gave an indication of efficacy against hospitalizations, the estimate was imprecise due to few hospitalized cases. Thus, the VE of a single dose of BNT162b2 in preventing hospital admission from COVID19 infection that was observed in very frail, co-morbid, elderly adults in this study was encouragingly high.

In contrast to a recent whole population data-linkage study from Scotland, which reported effectiveness estimates of 60-85% for one dose BNT162b2 against hospitalisation with

COVID19,[20] our study was restricted to the very elderly and adjusted for changes in exposure risk and groups targeted for vaccination over time. Our findings are in keeping with a preprint released by PHE, demonstrating a hazards ratio of 0.57 (0.58-0.67) of hospitalisation when undergoing COVID19 testing more than 14 days after BNT162b2 first dose.[7] Similarly, the SIREN study demonstrated a one dose BNT162b2 VE against hospitalisation of 72% (95% CI 58-86) at 21 days in younger healthcare workers.[21] SARI-Watch reported a one dose effectiveness of BNT162b2 of 57% (95% CI 48-63%) after first dose in adults ≥80.[22] A case control study from Israel found the estimated effectiveness of BNT162b2 against symptomatic disease in adults ≥70 years was 44% (95% CI 49-64) and 64% (95% CI 37-83) at 14-24 and 21-27 days following one dose, respectively.[3] In the same cohort, one dose BNT162b2 had an estimated effectiveness against hospitalisation of 74% (95% CI 56-86) and 78% (95% CI 61-91%) at 14-24 and 21-27 days post first dose.[3] Other studies from Israel reported one dose BNT162b2 has an effectiveness against COVID19 laboratory-confirmed infection of 51% at day 13-24,[23] or 75% at 15-28 days following first vaccine dose.[24] Taken together, our results and those released recently from other studies, suggest that, while substantial impact can be expected after only one dose of BNT162b2, even in high risk individuals, a second dose can be expected to provide valuable additional protection.

There is a paucity of real-world effectiveness data for one dose ChAdOx1nCoV-19 in preventing SARS-CoV-2 infection in elderly adults. This study reports estimated VE of a single dose ChAdOx1nCoV-19 against hospitalisation in elderly, frail adults using symptom onset to measure time disease started post-vaccination. Data released from PHE suggest a hazard ratio for ChAdOx1nCoV-19 of 0.63 (95% CI 0.41-0.97) in adults ≥80 years when SARS-CoV-19 testing was undertaken more than 14 days following first dose.[7] The results from this test-

negative case control study indicate single dose ChAdOx1nCoV-19 induces a very high level of protection against severe COVID19 disease in an elderly and frail real-world patient group.

A pooled analysis of four randomised trials reported one dose ChAdOx1nCoV-19 effectiveness against symptomatic disease from day 22-90 after first dose as 76·0% (95% CI 59·3–85·9).[5] Measurement of neutralising anti-spike IgG antibody levels following a single vaccine dose peaked at day 28 post vaccination. However, participants who received only a single ChAdOx1nCoV-19 dose had a median age 36·3 years (IQR 28·0-48·0), and were therefore much younger than this cohort.[4] Recently-released data from Scotland reported 74-94% effectiveness of one dose of ChAdOx1nCoV-19 against hospitalisation in that entire population between January and mid-February 2021.[20]

The point estimates for one dose effectiveness of each of the two vaccines evaluated in this study should not be compared with the other for several reasons. The 95% CIs overlap widely. Contrasting the cases in the two distinct vaccine analyses demonstrated several differences (Table 3). The Pfizer BNT162b2 vaccine was introduced when numbers of cases were rising but were considerably lower than case numbers in early January, when ChAdOx1nCoV-19 vaccination commenced. Perhaps more importantly, a sensitivity analysis restricting the observation period for BNT162b2 to the same period over which ChAdOx1nCoV-19 was studied, resulted in point estimates for the two vaccines that were almost identical (79.3% and 80.4%, respectively). This suggests that persons ≥80 years who received one dose of BNT162b2 in December may have been at greater COVID19 risk than individuals who received either vaccine in January. Thus, changes in vaccine deployment and hospital care which occurred during the study period may have biased results to some degree in the earliest

weeks of the programme. This may have included, but not been limited to: improvements in avoidance of vaccinating people already infected and, in some cases, symptomatic with COVID19; infection-control improvements in vaccination clinics; and, reduced exposure of individuals who had been successfully shielding themselves up to the time of immunisation.

Our study has several strengths. BNT162b2 and ChAdOx1nCoV-19 are available in the UK solely through the NHS without cost at the point of delivery, nor requirement for insurance. Thus, an individual's ability to pay for healthcare does not limit vaccine availability, and vaccinated adults are less likely to be wealthier compared to unvaccinated adults than in fee-based or insurance-based health systems.[25] Secondly, by undertaking a regression analysis adjusting for week of symptom onset we reduced the risk of bias attributable to any prioritisation that may have occurred in vaccination strategy or changes in background COVID19 rates and therefore exposure to infection. We also adjusted for socioeconomic status using IMD as this may affect likelihood of vaccine uptake, infection and severe disease rates.[26] Importantly, we utilised symptom onset date to define the start of illness and provide a time estimate following vaccination. We were therefore able to define illness start relative to both vaccine administration and hospitalisation accurately, not relying on date of first positive COVID19 test, eliminating bias or misclassification that may occur through use of test date alone which may vary widely. Finally, the observed ORs for both vaccines over the first 14 days after administration, when no protection was to be expected, although they had wide confidence interval, were both close to 1 suggesting that there was, at worst, only limited bias operating in these cohorts over the periods studied.

The current study has several limitations. First, we estimated VE of one dose against COVID19 related-hospitalisation and have not yet explored other secondary outcomes, including disease severity, hospital admission length and mortality. We expect to include effectiveness estimates against different circulating virus variants as time goes forward.[27] This study does not measure the effect of one dose in individuals who were not admitted to hospital with COVID19, and there may be treatment bias where elderly patients are not referred to hospital. This study provides VE estimates in secondary care settings only, not including General Practice or Accident and Emergency consultations which did not result in hospitalisation. Individuals who died before admission or who were otherwise not referred to hospital were not included in this study which therefore does not evaluate this subpopulation. General Practice or Accident and Emergency severe disease may have been included, and biased results towards lower vaccine effectiveness. It is also possible that weak or moderate protection induced by vaccination could result in slower disease progression and longer interval from onset to hospitalization for the vaccinated. Sampling and processing may have resulted both in false positive and negative PCR results which may have rendered the effectiveness estimates imprecise to some degree with uncertain direction and size of any such biases. Third, the study cohort was predominantly Caucasian and these vaccines may have different effectiveness in individuals from other ethnic backgrounds. This study specifically excluded individuals with asymptomatic disease and cannot determine the effectiveness of one vaccine dose against asymptomatic disease or transmission. We acknowledge this analysis has been conducted in one location on a small number of participants, and by necessity over a short time period.

We did not assess vaccine effectiveness against individual variants, and this was not being comprehensively tested on standard-of-care specimens during the study period. However, selective sequencing data indicate that almost all cases during the study period were B.1.1.7

with a small number of wild-type variants occurring. Finally, although we control for time in our analysis, we cannot fully account for temporal changes due to background exposure to infection, prevalence of variants of concern, or rising rates of vaccine receipt with emerging differences in characteristics between vaccine recipients and non-recipients in the study age range; a larger, individually-matched cohort study is indicated to control for these potential confounders better.

These results will help guide strategy development for BNT162b2 and ChAdOx1nCOV-19 vaccine use in clinical practice and should reassure policy makers of the high value of deploying these vaccines, and the importance of receipt of two doses, in elderly high-risk populations in whom incidence of severe disease and death from SARS-CoV-2 infection remains high.

Data Sharing

The data used in this study are sensitive and cannot be made publicly available without breaching patient confidentiality rules. Therefore, individual participant data and a data dictionary are not available to other researchers.

Contributors

CH, RM, LD, JO, and AF generated the research questions and analysis plan. CH, ZM, JK, LW, KF, RH, AT, ZF, LM, GR, RA, DA, MG, and ZSB were involved in data collection. CH and AF verified the data. CH, RM, LD, and AF undertook data analysis. All authors were involved in the final manuscript preparation and its revisions before publication. AF provided oversight of the research.

Declarations of Interest

CH is Principal Investigator of the Avon CAP study which is an investigator-led University of Bristol study funded by Pfizer and has previously received support from the NIHR in an Academic Clinical Fellowship. JO is a Co-Investigator on the Avon CAP Study. LD is further supported by UKRI through the JUNIPER consortium (grant number MR/V038613/1), MRC (grant number MC/PC/19067), EPSRC (EP/V051555/1 and The Alan Turing Institute, grant EP/N510129/1). AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) and chair of the World Health Organization European Technical Advisory Group of Experts on Immunization (ETAGE) committee. In addition to receiving funding from Pfizer as Chief Investigator of this study, he leads another project investigating transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates Foundation and is an

investigator in trials of COVID19 vaccines including ChAdOx1nCOV-19, Janssen and Valneva vaccines .The other authors have no relevant conflicts of interest to declare.

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Table One: Baseline characteristics of Cases and Controls in a Study of the Association of one dose of COVID-19 vaccination with SARS-CoV-2 infection Among Adults ≥80 years in Bristol, UK

Characteristic	Whole Cohort	BNT162b2 (Pfizer)			ChAdOx1nCoV-19 (Oxford-AstraZeneca)		
		Case N = 135	Control N = 269	*P*-value	Case N = 36	Control N = 90	*P*-value
Age (years) - median (IQR)	87·1 (83·6 - 90·9)	87·3 (83·3 - 90·7)	86·8 (83·8 - 90·7)	0·798	88·3 (84·2 - 90·6)	86·8 (84·1 - 91·7)	0·726
Male Gender – N (%)	234 (50·2 %)	66 (48·9 %)	133 (49·4 %)	>0·999	17 (47·2 %)	47 (52·2 %)	0·757
Care home resident – N (%)	97 (20·8 %)	30 (22·2 %)	44 (16·4 %)	0·193	12 (33·3 %)	21 (23·3 %)	0·353
Ethnicity – N (%)							
White British	404 (86·7 %)	118 (87·4 %)	237 (88·1 %)	0·967	27 (75·0 %)	75 (83·3 %)	0·409
Other	16 (3.4%)	6 (4.4%)	8 (3.0%)	0.498	< 5	< 5	0.644
Unknown	46 (9·9 %)	11 (8·1 %)	24 (8·9 %)	0·942	7 (19·4 %)	11 (12·2 %)	0·444
Smoking – N (%)							
Current	230 (49·4 %)	67 (49·6 %)	132 (49·1 %)	>0·999	14 (38·9 %)	45 (50·0 %)	0·352
Ex-smokers	11 (2·4 %)	< 5	7 (2·6 %)	0·717	< 5	< 5	>0·999
Comorbidity Scores – N (%)							
Rockwood Frailty 0-4	72 (15·5 %)	20 (14·8 %)	46 (17·1 %)	0·657	5 (13·9 %)	4 (4·4 %)	0·140
Rockwood Frailty 5-9	394 (84·5 %)	115 (85·2 %)	223 (82·9 %)	0·657	31 (86·1 %)	86 (95·6 %)	0·140
Charlson Comorbidity Index	5·0 (5·0 - 7·0)	6·0 (5·0 - 7·0)	5·0 (5·0 - 7·0)	0·347	5·0 (5·0 - 6·2)	5·0 (5·0 - 7·0)	0·403
Respiratory – N (%)							
Any	303 (65·0 %)	94 (69·6 %)	171 (63·6 %)	0·272	30 (83·3 %)	53 (58·9 %)	0·016
Chronic Obstructive Pulmonary Disease	109 (23·4 %)	30 (22·2 %)	62 (23·0 %)	0·951	5 (13·9 %)	25 (27·8 %)	0·155
Asthma	47 (10·1 %)	9 (6·7 %)	31 (11·5 %)	0·172	< 5	10 (11·1 %)	0·533
Other *	37 (7·9 %)	5 (3·7 %)	26 (9·7 %)	0·054	0 (0·0 %)	12 (13·3 %)	0·049
Cardiovascular							
Any	283 (60·7 %)	83 (61·5 %)	164 (61·0 %)	>0·999	22 (61·1 %)	56 (62·2 %)	>0·999
Ischaemic Heart Disease	110 (23·6 %)	22 (16·3 %)	68 (25·3 %)	0·055	6 (16·7 %)	27 (30·0 %)	0·189
Atrial Fibrillation	122 (26·2 %)	40 (29·6 %)	69 (25·7 %)	0·465	6 (16·7 %)	25 (27·8 %)	0·280

Characteristic	Whole Cohort	BNT162b2 (Pfizer)			ChAdOx1nCoV-19 (Oxford-AstraZeneca)		
		Case N = 135	Control N = 269	*P*-value	Case N = 36	Control N = 90	*P*-value
Congestive Cardiac Failure	103 (22·1 %)	30 (22·2 %)	61 (22·7 %)	>0·999	5 (13·9 %)	22 (24·4 %)	0·287
Diabetes – N (%)							
Any	97 (20·8 %)	34 (25·2 %)	51 (19·0 %)	0·187	9 (25·0 %)	18 (20·0 %)	0·706
Type 1 Diabetes Mellitus	< 5	< 5	< 5	>0·999	0 (0·0 %)	0 (0·0 %)	NA
Type 2 Diabetes Mellitus	96 (20·6 %)	34 (25·2 %)	50 (18·6 %)	0·158	9 (25·0 %)	18 (20·0 %)	0·706
Neurological – N (%)							
Dementia	55 (11·8 %)	20 (14·8 %)	26 (9·7 %)	0·170	5 (13·9 %)	12 (13·3 %)	>0·999
Cognitive Impairment	57 (12·2 %)	18 (13·3 %)	33 (12·3 %)	0·884	5 (13·9 %)	8 (8·9 %)	0·610
Cerebrovascular Accident	55 (11·8 %)	13 (9·6 %)	32 (11·9 %)	0·606	< 5	15 (16·7 %)	0·174
Transient Ischaemic Attack	33 (7·1 %)	9 (6·7 %)	19 (7·1 %)	>0·999	< 5	5 (5·6 %)	>0·999
Other Neurological disease ‡	19 (4·1 %)	8 (5·9 %)	8 (3·0 %)	0·244	< 5	< 5	>0·999
Oncology – N (%)							
Solid Organ Cancer	37 (7·9 %)	10 (7·4 %)	21 (7·8 %)	>0·999	< 5	7 (7·8 %)	0·803
Haematological Malignancy	14 (3·0 %)	7 (5·2 %)	6 (2·2 %)	0·198	< 5	< 5	0·942
Renal disease† – N (%)							
Mild	178 (38·2 %)	53 (39·3 %)	96 (35·7 %)	0·554	14 (38·9 %)	40 (44·4 %)	0·711
Moderate/Severe	32 (6·9 %)	13 (9·6 %)	18 (6·7 %)	0·396	< 5	5 (5·6 %)	0·862

* Includes bronchiectasis, pulmonary fibrosis, and other chronic respiratory conditions

‡ Includes Parkinson's disease, Huntingdon's disease, and other chronic neurological conditions

† Mild = chronic kidney disease stage 1-3; Moderate/Severe = chronic kidney disease stage 4-5, end-stage renal failure or dialysis dependence

In order to maintain patient confidentiality, figures have been modified to show <5

Table Two: Vaccine effectiveness for one dose of BNT162b2 and ChAdOx1nCoV-19 in adults ≥80 years in Bristol, UK

Analysis	Factor	VE (95% CI)	OR (95% CI)	*P*-value
One dose BNT162b2 (Pfizer)				
Unadjusted	-	69.4 (47.7-82.9)	0.306 (0.171-0.523)	<0.0001
Logistic Regression Model	One dose	71.4 (43.1-86.2)	0.286 (0.138-0.569)	<0.0001
	Care home	-	1.551 (0.900-2.654)	0.1105
	Gender (male)	-	1.069 (0.694-1.649)	0.7605
	Week	-	1.023 (0.923-1.134)	0.6667
	IMD	-	0.913 (0.848-.0982)	0.0152
Matched Conditional Regression Model a	One dose	57.4 (-0.20-81.9)	0.426 (0.181-1.002)	0.0505
	Care home	-	1.778 (0.966-3.271)	0.0643
	IMD	-	0.929 (0.861-1.004)	0.0618
Unadjusted, <14 days	-	6.5 (-65.8-48.2)	0.935 (0.518-1.658)	0.8200
One dose ChAdOx1nCoV-19 (Oxford-AstraZeneca)				
Unadjusted	-	76.7 (46.5-90.6)	0.233 (0.094-0.535)	<0.0001
Logistic Regression Model	One dose	80.4 (36.4-94.5)	0.196 (0.055-0.636)	0.0083
	Care home	-	3.181 (1.160-9.345)	0.0276
	Gender (male)	-	0.949 (0.407-2.204)	0.9022
	Week	-	0.934 (0.650-1.336)	0.7066
	IMD	-	0.914 (0.784-1.061)	0.2413
Matched Conditional Regression Model b	One dose	73.3 (-6.1-93.2)	0.267 (0.067-1.061)	0.0601
	Care home	-	2.837 (0.806-9.985)	0.1043
	IMD	-	0.937 (0.798-1.098)	0.4203
Unadjusted, <14 days	-	-12.6 (-136.9-46.5)	1.126 (0.535-2.369)	0.7545

a 129 cases were matched to 187 controls with no match found for 6 cases and 82 controls

b 32 cases were matched to 52 controls with no match found for 4 cases and 38 controls

IMD, Index of Multiple Deprivation; OR, odds ratio; VE, vaccine effectiveness

† VE for one dose BNT162b2 calculated from 8th December 2020 until 26th February 2021

‡ VE for one dose ChAdOx1nCoV-19 calculated from 4th January 2021 until 26th February 2021

72 **Table Three:** Characteristics of individuals within the cases and controls who received one
73 dose of either BNT162b2 or ChAdOx1nCoV-19

Characteristic	BNT162b2 (Pfizer) N = 108	ChAdOx1nCoV-19 (Oxford-AstraZeneca) N = 62	*P*-value
Age (years) - median (IQR)	86·4 (83·5 - 90·2)	87·5 (84·0 - 91·8)	0·287
Male Gender – N (%)	64 (59·3 %)	35 (56·5 %)	0·845
Care home resident – N (%)	21 (19·4 %)	23 (37·1 %)	0·019
Ethnicity – N (%)			
White British	93 (86·1 %)	49 (79·0 %)	0·326
Other	< 5	< 5	NA
Unknown	12 (11·1 %)	11 (17·7 %)	0·325
Smoking – N (%)			
Current	47 (43·5 %)	31 (50·0 %)	0·512
Ex-smokers	< 5	< 5	>0·999
Comorbidity Scores – N (%)			
Rockwood Frailty 0-4	29 (26·9 %)	6 (9·7 %)	0·014
Rockwood Frailty 5-9	79 (73·1 %)	56 (90·3 %)	0·014
Charlson Comorbidity Index	5·0 (4·0 - 6·0)	5·5 (5·0 - 6·8)	0·355
Respiratory – N (%)			
Any	73 (67·6 %)	38 (61·3 %)	0·507
Chronic Obstructive Pulmonary Disease	18 (16·7 %)	17 (27·4 %)	0·141
Asthma	15 (13·9 %)	7 (11·3 %)	0·804
Other *	6 (5·6 %)	6 (9·7 %)	0·485
Cardiovascular			
Any	66 (61·1 %)	36 (58·1 %)	0·820
Ischaemic Heart Disease	23 (21·3 %)	20 (32·3 %)	0·162
Atrial Fibrillation	32 (29·6 %)	13 (21·0 %)	0·293
Congestive Cardiac Failure	23 (21·3 %)	12 (19·4 %)	0·917
Diabetes – N (%)			
Any	21 (19·4 %)	12 (19·4 %)	>0·999
Type 1 Diabetes Mellitus	< 5	< 5	>0·999
Type 2 Diabetes Mellitus	20 (18·5 %)	12 (19·4 %)	>0·999
Neurological – N (%)			
Dementia	11 (10·2 %)	9 (14·5 %)	0·551
Cognitive Impairment	10 (9·3 %)	6 (9·7 %)	>0·999
Cerebrovascular Accident	13 (12·0 %)	10 (16·1 %)	0·605
Transient Ischaemic Attack	6 (5·6 %)	5 (8·1 %)	0·752
Other Neurological disease ‡	< 5	< 5	>0·999
Oncology – N (%)			
Solid Organ Cancer	9 (8·3 %)	6 (9·7 %)	0·987
Haematological Malignancy	< 5	< 5	>0·999
Renal disease† – N (%)			

Mild	35 (32·4 %)	29 (46·8 %)	0·090
Moderate/Severe	5 (4·6 %)	< 5	0·552

* Includes bronchiectasis, pulmonary fibrosis, and other chronic respiratory conditions

‡ Includes Parkinson's disease, Huntingdon's disease, and other chronic neurological conditions

† Mild = chronic kidney disease stage 1-3; Moderate/Severe = chronic kidney disease stage 4-5, end-stage renal failure or dialysis dependence

In order to maintain patient confidentiality, figures have been modified to show <5

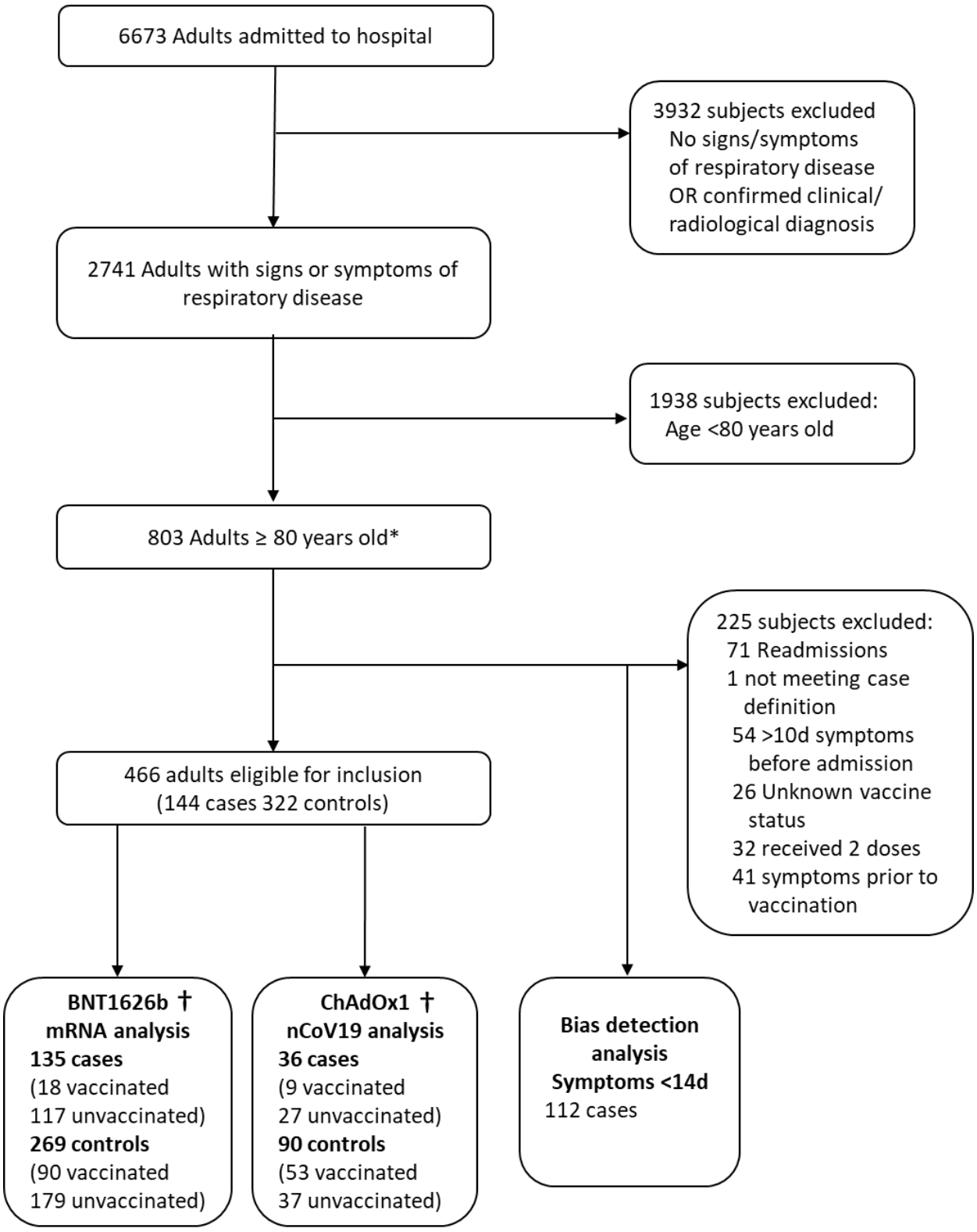

Figure One: Study Diagram

(A) Flow diagram showing the total study cohort of 144 SARS-CoV-2 positive cases divides into 135 BNT1626b vaccinated and unvaccinated cases and 9 ChAdOx1nCoV-19 vaccinated cases with the 27 unvaccinated cases in ChAdOx1 arm shared from the unvaccinated cases in the BNT1626b arm.

- Aged ≥80 years by 31/03/2021

† further details of the cases and controls can be found in the Euler diagram, Figure 2

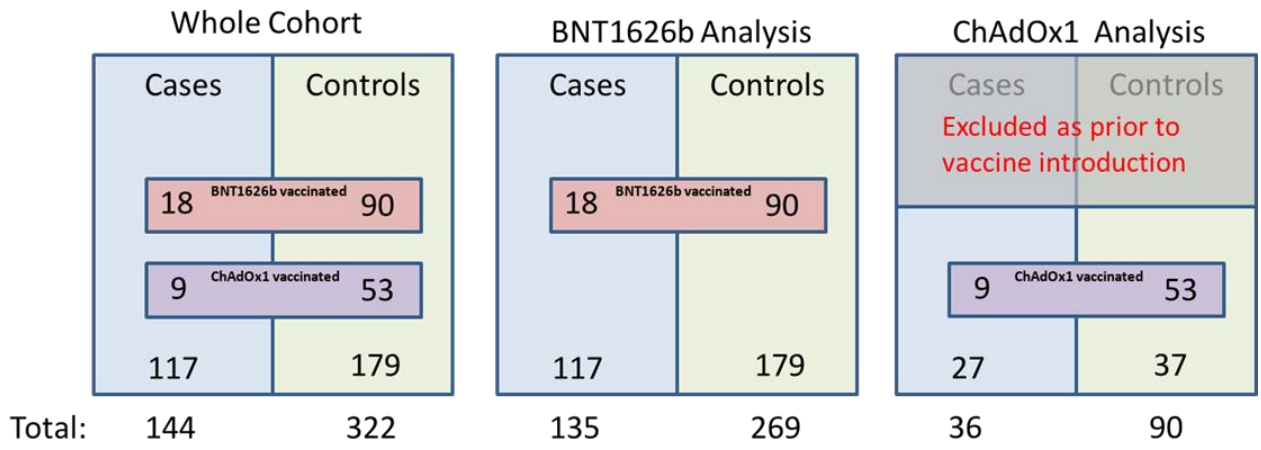

Figure 2: Euler diagram of study cohorts

Demonstrates how total study cohort of 144 SARS-CoV-2 positive cases and 322 SARS-CoV-2 negative controls divide into the BNT1626b 135 cases / 269 controls and ChAdOx1nCoV-19 36 cases / 90 controls. The ChAdOx1nCoV-19 arm is smaller due to the later introduction of this vaccine (4/1/21), thus only the subset of controls identified after this date were eligible for this analysis.

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