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Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study

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Summary

Background On Dec 8, 2020, deployment of the first SARS-CoV-2 vaccination authorised for UK use (BNT162b2 mRNA vaccine) began, followed by an adenoviral vector vaccine ChAdOx1 nCoV-19 on Jan 4, 2021. Care home residents and staff, frontline health-care workers, and adults aged 80 years and older were vaccinated first. However, few data exist regarding the effectiveness of these vaccines in older people with many comorbidities. In this post-implementation evaluation of two COVID-19 vaccines, we aimed to determine the effectiveness of one dose in reducing COVID-19-related admissions to hospital in people of advanced age.

Methods This prospective test-negative case-control study included adults aged at least 80 years who were admitted to hospital in two NHS trusts in Bristol, UK with signs and symptoms of respiratory disease. Patients who developed symptoms before receiving their vaccine or those who received their vaccine after admission to hospital were excluded, as were those with symptoms that started more than 10 days before hospital admission. We did logistic regression analysis, controlling for time (week), sex, index of multiple deprivations, and care residency status, and sensitivity analyses matched for time and sex using a conditional logistic model adjusting for index of multiple deprivations and care residency status. This study is registered with ISRCTN, number 39557.

Findings Between Dec 18, 2020, and Feb 26, 2021, 466 adults were eligible (144 test-positive and 322 test-negative). 18 (13%) of 135 people with SARS-CoV-2 infection and 90 (34%) of 269 controls received one dose of BNT162b2. The adjusted vaccine effectiveness was 71·4% (95% CI 46·5–90·6). Nine (25%) of 36 people with COVID-19 infection and 53 (59%) of 90 controls received one dose of ChAdOx1 nCoV-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 ChAdOx1 nCoV-19, the estimate was 79·3% (95% CI 47·0–92·5).

Interpretation One dose of either BNT162b2 or ChAdOx1 nCoV-19 resulted in substantial risk reductions of COVID-19-related hospitalisation in people aged at least 80 years.

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Introduction

SARS-CoV-2 has resulted in a global pandemic with over 153 954 491 cases and 3 221 052 deaths as of May 6, 2021.[1] The authorisation of several vaccines has followed multiple international randomised controlled trials. As of April 1, 2021, two vaccinations against SARS-CoV-2 are in use in the UK: an mRNA-based vaccine (BNT162b2; tozinameran) produced by Pfizer Inc and BioNTech SE and a replication-deficient simian adenovirus vector ChAdOx1 nCoV-19 (Vaxzevria) 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 of BNT162b2 have 95% (95% CI 90–98) efficacy at least 7 days after the second dose against symptomatic SARS-CoV-2 infection in participants without evidence of previous COVID-19 infection.[2] Early in 2021, researchers reported that BNT162b2 has an effectiveness of 73% (95% CI 62–82) at 21–27 days after the first dose against symptomatic disease in people older than 70 years in Israel.[3] After two doses, ChAdOx1 nCoV-19 has 70% efficacy at least 14 days after the 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 that neutralising antibodies are detectable 28 days after a single ChAdOx1 nCoV-19 dose in adults aged at least 70 years.[6] Data from Public Health England (PHE) show a relative risk of hospitalisation, more than 14 days after first dose, of 0·57 (95% CI 0·48–0·67) for BNT162b2 and 0·63 (0·41–0·97) for ChAdOx1 nCoV-19 in people aged at least 80 years, when using date of first positive test and of admission to hospital.[7]

Research in context

Evidence before this study

We searched PubMed and medRxiv for observational studies published between Dec 1, 2020, and Feb 10, 2021, using the terms "COVID19 vaccine effect", "SARS-CoV-2" or "COVID-19", "vaccine", and "effectiveness". We selected articles with no language restrictions. Our search returned five studies, all of which were relevant to this topic. A case-control study found one dose of BNT162b2 has an estimated effectiveness against symptomatic disease in people aged 70 years and older of 62% (95% CI 43–77) at 14–21 days after first dose and 73% (95% CI 62-82) at 21–27 days after first dose. A paper authored by Public Health England employees using positive testing reported 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 aged at least 80 years with BNT162b2 or ChAdOx1 nCoV-19 respectively. A preprint reported one dose vaccine effectiveness against hospitalisation of 85% (95% CI 76–91) and 94% (73–99) 28–34 days after first dose BNT162b2 and ChAdOx1 nCoV-19 respectively, and in adults aged at least 80 years 81% (65-90) for the two 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 health-care workers with a median age of 46·1 years reported vaccine effectiveness of 70% (95% CI 55–85) 21 days after first dose of BNT162b2 against SARS-CoV-2 infection (symptomatic and asymptomatic).

Added value of this study

To date, few real-world data exist on the effectiveness of one dose of the BNT162b2 or ChAdOx1 nCoV-19 vaccines, and data for the effectiveness of ChAdOx1 nCoV-19 against COVID-19 disease are scarce in people aged at least 70 years. This test-negative, case-control study reports the effect of one dose of BNT162b2 or ChAdOx1 nCoV-19 vaccine against admission to hospital in people aged at least 80 years, who were often frail and had comorbidities, 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

Our findings provide evidence that one dose of either the BNT162b2 or ChAdOx1 nCoV-19 vaccine, currently used in the UK vaccination programme, substantially reduces the risk of COVID-19-related hospital admissions, in individuals aged at least 80 years old on March 31, 2021.

The UK Medicines & Healthcare Products Regulatory Agency granted the first use authorisation worldwide for BNT162b2 on Dec 2, 2020.[8] The UK national BNT162b2 vaccination programme started on Dec 8, 2020. Authorisation for ChAdOx1 nCoV-19 followed on Dec 30, 2020, with first administration of ChAdOx1 nCoV-19 on Jan 4, 2021. The Joint Committee on Vaccination and Immunisation (JCVI) advised targeting vaccines towards those at highest risk of severe disease: residents in long-term care facilities (LTCFs) and their carers, patients aged at least 80 years, and frontline health and social care workers.[9] However, several other European countries have deferred ChAdOx1 nCoV-19 vaccination in adults older than either 55 or 65 years owing to the absence of efficacy or effectiveness evidence in those age groups, despite high infection and hospitalisation incidences.

After administration of both vaccines had begun, the JCVI advised delaying second dose administration, enabling the prioritisation of the first vaccine dose to increase the short-term public health impact of vaccination and reduce preventable deaths. Whilst maintaining support for a two-dosing regimen, the JCVI recommended extending the maximum interval between doses from 3 weeks (BNT162b2) and 4 weeks (ChAdOx1 nCoV-19) to 12 weeks for both vaccinations.[10] In the context of these policies, this test-negative case-control study aimed to assess the effectiveness of a single BNT162b2 or ChAdOx1 nCoV-19 vaccine dose against COVID-19-related admissions to hospital for people aged at least 80 years in Bristol, UK.

Methods

Study design and participants

We did a test-negative case-control study[11,12] of consecutive adults admitted to one hospital (Southmead Hospital) in North Bristol NHS Trust or one hospital (Bristol Royal Infirmary) in University Hospitals Bristol and Weston NHS Foundation Trust with signs and symptoms of respiratory disease between Dec 18, 2020 (ie, 10 days after administration of BNT162b2 started), and Feb 26, 2021, inclusive. Enrolment started at this time point because the Kaplan-Meier graph in the phase 3 BNT162b2 study showed divergence between controls and vaccinees from 10 days post-vaccination.[2] Patients with signs and symptoms of respiratory infection and who would be aged at least 80 years on March 31, 2021 (ie, the age group initially targeted for vaccination) were included in this analysis. A clinician identified eligible test-positive and test-negative individuals 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 the test-positive and test-negative groups. To avoid observer bias, all data were collected by individuals who were not involved in data analysis and blinded to the results.

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

This study was approved by the Health Research Authority Research Ethics Committee (East of England, Essex, UK), including data collection under Section 251 of the 2006 NHS Act authorised by the Confidentiality Advisory Group.

All adults admitted to the two participating hospitals—which encompass all the acute adult secondary care facilities in Bristol—were screened for signs and symptoms of respiratory disease, including: documented fever (≥38°C) or hypothermia (<35·5°C); cough; increased sputum volume or sputum discolouration; pleurisy; dyspnoea; tachypnoea; examination findings compatible with acute lower respiratory tract disease (eg, crepitations); or radiological changes suggestive of acute respiratory tract disease. Patients with at least two of these signs, or a confirmed clinical or radiological diagnosis of acute lower respiratory tract disease, were included.

Patients who developed symptoms before receiving their vaccine or those who received their vaccine after admission were excluded, as were those with symptoms that started more than 10 days before admission to avoid including patients with potentially false negative admission SARS-CoV-2 tests. To avoid bias due to nosocomial infection, readmissions data were excluded (ie, only the first admission of each patient was counted).

Test-positive individuals were defined as having symptomatic respiratory disease and a positive admission result for SARS-CoV-2, using Hologic Panther TMA assay done by PHE diagnostic laboratories.[14] Test-negative individuals (controls) had to have respiratory disease and a negative SARS-CoV-2 result.

Procedures

We studied the effectiveness of the first dose of BNT162b2 (Pfizer) vaccine and ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine. Individuals were defined as exposed if they had received a single dose of either vaccine between Dec 8, 2020 (Pfizer) or Jan 4, 2021 (Oxford–AstraZeneca), and Feb 12, 2021, with recruitment censored between Feb 26, 2021, and the latest event date. Unvaccinated or unexposed individuals in the analyses had received neither vaccine.

For each participant, we collected data on co-morbidities at the time of admission and determined their Charlson co-morbidity index (CCI; with published estimates of 10-year survival)[15] and Rockwood clinical frailty score (with a score of 5–9 indicating frailty).[16]

Outcomes

Our primary outcome was the vaccine effectiveness of first doses against hospital admissions with respiratory infection. Vaccine effectiveness of first dose was assessed at least 14 days after receipt of first dose. Those developing symptoms within 14 days of receipt of first vaccine dose were excluded from the primary analysis but were assessed in a separate bias detection analysis (negative control).

Statistical analysis

Before study initiation, we calculated the necessary sample size to ensure feasibility.[17,18] Although this calculation was sensitive to vaccine uptake in controls, we predicted that, with 80% power and a two-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 test-positive individuals.

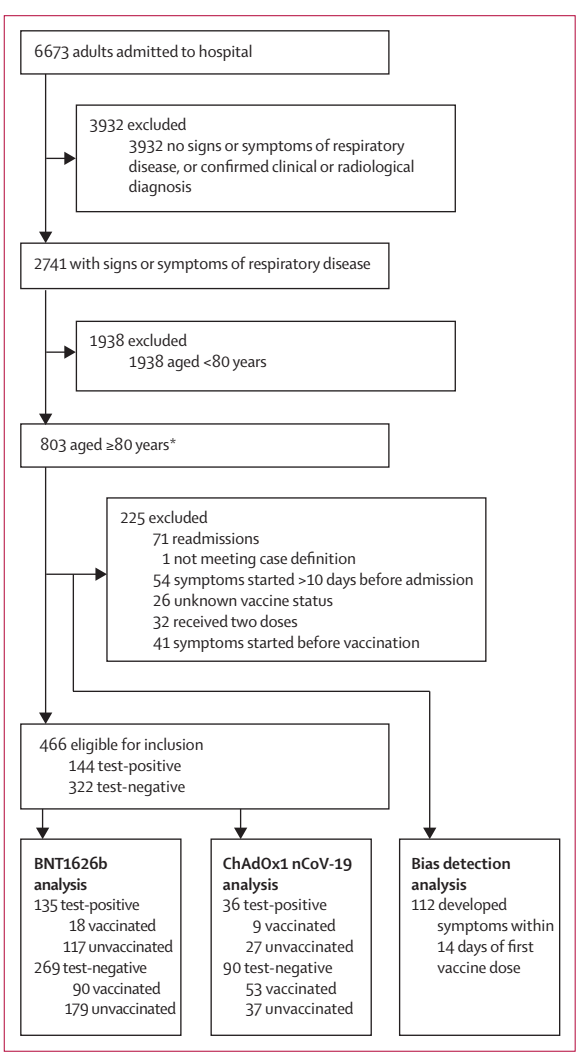

Figure 1: **Study profile**
Total study cohort of 144 SARS-CoV-2-positive individuals divides into 135 BNT1626b vaccinated and unvaccinated cases and nine ChAdOx1 nCoV-19 vaccinated cases, with the 27 unvaccinated cases in the ChAdOx1 nCoV-19 group shared from the unvaccinated cases in the BNT1626b group. *Aged at least 80 years by March 31, 2021.

Vaccine effectiveness was defined as 1–OR of receipt of one dose. We compared the proportion of test-positive individuals who received one dose with that in controls using adjusted and unadjusted regression analyses. Due to the evolving nature of both the COVID-19 epidemic and rollout of the vaccine programme, we recognise that changes over time could introduce biases and confound results. To mitigate this, we used unmatched logistic regression analyses, with adjustment for week of symptom onset, sex, LTCF residency status, and decile rank of index of multiple deprivations. We also did an additional analysis matching test-positive and test-negative individuals by sex and week of symptom onset, and we adjusted for deprivation and LTCF residency status using conditional logistic regression.[19] Finally, to explore the possible effect of instabilities during the first weeks of the vaccine programme, we analysed the apparent effectiveness of BNT162b2 during the period in early 2021 when ChAdOx1 nCoV-19 was also used (between Jan 4, and Feb 26, 2021). To assess likely levels of residual bias, we did a negative control analysis in which we calculated the apparent effectiveness of one dose of vaccine during the period up to 14 days after administration, when no protection was expected. Analyses for each vaccine were done separately.

We compared proportions using Fisher exact tests and compared parametric data using Student's t-tests. We used R (version 4.0.2) for all statistical analyses. Regarding missing data, we planned to exclude participants for whom vaccine status could not be determined. Statistical significance was defined using two-sided significance level of $\alpha=0\cdot05$.

This study is registered with ISRCTN, number 39557.

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, or writing of the report.

Results

By Feb 12, 2021, National Immunisation Management Service data showed that 44 844 (95·0%) of 47 355 people who were aged at least 80 years and residents in Bristol, UK, had received their first dose of a COVID-19 vaccine.[20] Between Dec 18, 2020, and Feb 26, 2021, 6673 adults (aged ≥18 years) were admitted to participating hospitals in Bristol (figure 1). 2741 had signs or symptoms of respiratory disease; of whom 803 (29%) were aged at least 80 years and 466 were enrolled. Missing data were minimal; vaccine status could not be determined for 26 patients (figure 1). No imputation was done. 144 (31%) of 466 enrolled patients tested positive for SARS-CoV-2. The designation of test-positive and test-negative groups is shown in figure 2. The period of observation from vaccination to data cutoff (Feb 26, 2021) for this analysis was 34–80 days for BNT162b2 and 19–64 days for ChAdOx1 nCoV-19.

Among people in the BNT162b2 analysis with confirmed COVID-19, median age was 87·3 years (IQR 83·3– 90·7), 69 (51%) were female, and 30 (22%) lived in a LTCF (table 1). 115 (85%) were classified as frail on the Rockwood clinical frailty score, and the median CCI was 6·0 (IQR 5·0-7·0), with published estimates of 10-year survival under 30%.[15]

108 individuals received a single dose of BNT162b2 vaccination more than 14 days before symptom onset. 18 (13%) of the 135 people with SARS-CoV-2 infection and 90 (34%) of 269 controls received one dose BTN162b2 (difference –20·2%), giving an unadjusted vaccine effectiveness of 69·4% (95% CI 47·7–82·9) and an adjusted effectiveness of 71·4% (43·1–86·2; table 2). Care home status did not substantially alter the vaccine effectiveness results. Matched conditional sensitivity analysis generated a slightly lower effectiveness estimate, with wider confidence intervals that crossed zero, owing to imperfect matching (table 2). Imperfect matching occurred if at each timepoint one group is already entirely matched and there were consequently leftover test-positive or test-negative individuals. The OR for unadjusted vaccine effectiveness up to 14 days from

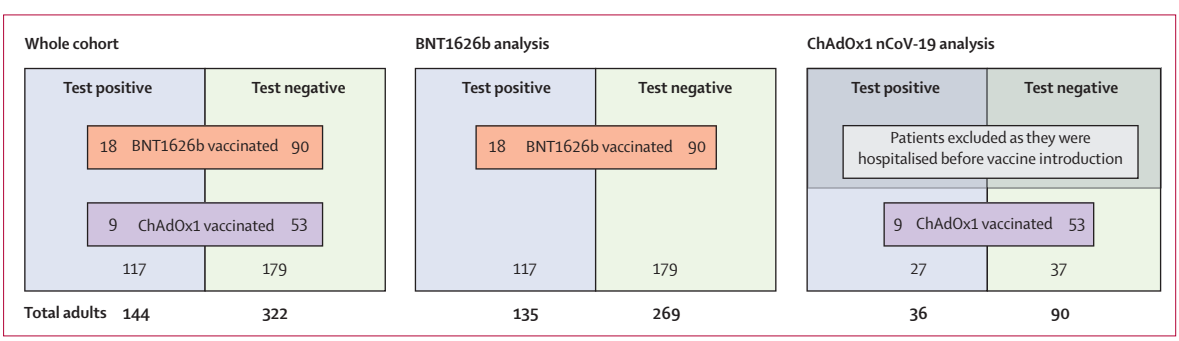

Figure 2: **Euler diagram of study cohorts**
Total study cohort of 144 SARS-CoV-2-positive cases and 322 SARS-CoV-2-negative controls, separated into the BNT1626b group (135 test-positive and 269 test-negative) and ChAdOx1 nCoV-19 group (36 test-positive and 90 test-negative). The ChAdOx1 nCoV-19 group is smaller due to the later introduction of this vaccine (on Jan 4, 2021), thus only the subset of controls identified after this date were eligible for this analysis.

vaccination until symptom onset was 0·935, suggesting that bias was low in the BNT162b2 cohort.

Among people in the ChAdOx1 nCoV-19 analysis with confirmed COVID-19, median age was 88·3 (IQR 84·2–90·6), 19 (53%) were female, and 12 (33%) were residents in LTCFs (table 1). 31 (86%) were classified as frail on the Rockwood clinical frailty score, and the median CCI was 5·0 (IQR 5·0–6·2),

	Whole cohort	BNT162b2 (Pfizer)			ChAdOx1 nCoV-19 (Oxford–AstraZeneca)		
		Test-positive group (n=135)	Test-negative group (n=269)	p value	Test-positive group (n=36)	Test-negative group (n=90)	p value
Age, median years (IQR)	87·1 (83·6–90·9)	87·3 (83·3–90·7)	86·8 (83·8–90·7)	0·80	88·3 (84·2–90·6)	86·8 (84·1–91·7)	0·73
Sex							
Female	232 (50%)	69 (51%)	136 (51%)	>0·99	19 (53%)	43 (48%)	0·76
Male	234 (50%)	66 (49%)	133 (49%)	>0·99	17 (47%)	47 (52%)	0·76
Long-term care facility resident	97 (21%)	30 (22%)	44 (16%)	0·19	12 (33%)	21 (23%)	0·35
Ethnicity							
White British	404 (87%)	118 (87%)	237 (88%)	0·97	27 (75%)	75 (83%)	0·41
Other	16 (3%)	6 (4%)	8 (3%)	0·50	<5	<5	0·64
Unknown	46 (10%)	11 (8%)	24 (9%)	0·94	7 (19%)	11 (12%)	0·44
Smoking							
Current	230 (49%)	67 (50%)	132 (49%)	>0·99	14 (39%)	45 (50%)	0·35
Ex-smokers	11 (2%)	<5	7 (3%)	0·72	<5	<5	>0·99
Comorbidity scores							
Rockwood clinical frailty scale							
0–4	72 (16%)	20 (15%)	46 (17%)	0·66	5 (14%)	4 (4%)	0·14
5–9	394 (85%)	115 (85%)	223 (83%)	0·66	31 (86%)	86 (96%)	0·14
Charlson comorbidity index	5·0 (5·0–7·0)	6·0 (5·0–7·0)	5·0 (5·0–7·0)	0·35	5·0 (5·0–6·2)	5·0 (5·0–7·0)	0·40
Respiratory							
Any	303 (65%)	94 (70%)	171 (64%)	0·27	30 (83%)	53 (59%)	0·02
Chronic obstructive pulmonary disease	109 (23%)	30 (22%)	62 (23%)	0·95	5 (14%)	25 (28%)	0·16
Asthma	47 (10%)	9 (7%)	31 (12%)	0·17	<5	10 (11%)	0·53
Other*	37 (8%)	5 (4%)	26 (10%)	0·05	0	12 (13%)	0·05
Cardiovascular							
Any	283 (61%)	83 (62%)	164 (61%)	>0·99	22 (61%)	56 (62%)	>0·99
Ischaemic heart disease	110 (24%)	22 (16%)	68 (25%)	0·06	6 (17%)	27 (30%)	0·19
Atrial fibrillation	122 (26%)	40 (30%)	69 (26%)	0·47	6 (17%)	25 (28%)	0·28
Congestive cardiac failure	103 (22%)	30 (22%)	61 (23%)	>0·99	5 (14%)	22 (24%)	0·29
Diabetes							
Any	97 (21%)	34 (25%)	51 (19%)	0·19	9 (25%)	18 (20%)	0·71
Type 1	<5	<5	<5	>0·99	0	0	NA
Type 2	96 (21%)	34 (25%)	50 (19%)	0·16	9 (25%)	18 (20%)	0·71
Neurological							
Dementia	55 (12%)	20 (15%)	26 (10%)	0·17	5 (14%)	12 (13%)	>0·99
Cognitive impairment	57 (12%)	18 (13%)	33 (12%)	0·88	5 (14%)	8 (9%)	0·61
Cerebrovascular accident	55 (12%)	13 (10%)	32 (12%)	0·61	<5	15 (17%)	0·17
Transient ischaemic attack	33 (7%)	9 (7%)	19 (7%)	>0·99	<5	5 (6%)	>0·99
Other neurological disease†	19 (4%)	8 (6%)	8 (3%)	0·24	<5	<5	>0·99
Oncology							
Solid organ cancer	37 (8%)	10 (7%)	21 (8%)	>0·99	<5	7 (8%)	0·80
Haematological malignancy	14 (3%)	7 (5%)	6 (2%)	0·20	<5	<5	0·94
Renal disease‡							
Mild	178 (38%)	53 (39%)	96 (36%)	0·55	14 (39%)	40 (44%)	0·71
Moderate or severe	32 (7%)	13 (10%)	18 (7%)	0·40	<5	5 (6%)	0·86

Data are n (%) unless otherwise stated. To maintain patient confidentiality, data with fewer than five patients have been amended to <5. *Includes bronchiectasis, pulmonary fibrosis, and other chronic respiratory conditions. †Includes Parkinson's disease, Huntingdon's disease, and other chronic neurological conditions. ‡Mild is chronic kidney disease stage 1–3; moderate or severe is chronic kidney disease stage 4–5, end-stage renal failure, or dialysis dependence.

Table 1: **Baseline characteristics of study cohort**

	Vaccine effectiveness (95% CI)	Odds ratio (95% CI)	p value
One dose of BNT162b2 (Pfizer)			
Unadjusted	69·4 (47·7 to 82·9)	0·306 (0·171–0·523)	<0·0001
Logistic regression model			
One dose	71·4 (43·1 to 86·2)	0·286 (0·138–0·569)	<0·0001
Long-term care facility resident	..	1·551 (0·900–2·654)	0·11
Sex (male)	..	1·069 (0·694–1·649)	0·76
Week	..	1·023 (0·923–1·134)	0·67
IMD	..	0·913 (0·848–0982)	0·015
Matched conditional regression model*			
One dose	57·4 (–0·20 to 81·9)	0·426 (0·181–1·002)	0·051
Long-term care facility resident	..	1·778 (0·966–3·271)	0·064
IMD	..	0·929 (0·861–1·004)	0·062
Unadjusted, within 14 days of symptom onset	6·5 (–65·8 to 48·2)	0·935 (0·518–1·658)	0·82
One dose of ChAdOx1 nCoV-19 (Oxford–AstraZeneca)			
Unadjusted	76·7 (46·5 to 90·6)	0·233 (0·094–0·535)	<0·0001
Logistic regression model			
One dose	80·4 (36·4 to 94·5)	0·196 (0·055–0·636)	0·0083
Long-term care facility resident	..	3·181 (1·160–9·345)	0·028
Sex (male)	..	0·949 (0·407–2·204)	0·90
Week	..	0·934 (0·650–1·336)	0·71
IMD	..	0·914 (0·784–1·061)	0·24
Matched conditional regression model†			
One dose	73·3 (–6·1 to 93·2)	0·267 (0·067–1·061)	0·06
Long-term care facility resident	..	2·837 (0·806–9·985)	0·10
IMD	..	0·937 (0·798–1·098)	0·42
Unadjusted, within 14 days of symptom onset	–12·6 (–136·9 to 46·5)	1·126 (0·535–2·369)	0·75

IMD=index of multiple deprivation. *129 test-positive cases were matched to 187 test-negative controls with no match found for six cases and 82 controls. For one dose of BNT162b2 between Dec 8, 2020, and Feb 26, 2021. †32 test-positive cases were matched to 52 test-negative controls with no match found for four cases and 38 controls. For one dose of ChAdOx1 nCoV-19 between Jan 4, 2021, and Feb 26, 2021.

Table 2: **Vaccine effectiveness for one dose of BNT162b2 or ChAdOx1 nCoV-19**

with published estimates of 10-year survival under 30%.[15]

62 individuals received a single dose of ChAdOx1 nCoV-19 vaccination more than 14 days before symptom onset. Nine (25%) of the 36 people with SARS-CoV-2 infection and 53 (59%) of 90 controls received one dose of ChAdOx1 nCoV-19 (difference –33·9%), giving an unadjusted vaccine effectiveness of 76·7% (95% CI 46·5–90·6) and adjusted effectiveness of 80·4% (36·4–94·5; table 2). Care home status did not substantially alter the vaccine effectiveness results. Consistent with the BNT162b2 analysis, matched conditional sensitivity analysis again generated a slightly lower estimate, with wider confidence intervals that crossed zero. Unadjusted vaccine effectiveness up to 14 days from vaccination until symptom onset was close to zero (OR 1·13); since this outcome is the expected biological reality, our finding suggests that bias was low in the ChAdOx1 nCoV-19 cohort.

Due to vaccine delivery logistics in Bristol and other parts of the UK, compared with those vaccinated with ChAdOx1 nCoV-19, recipients of BNT162b2 were significantly less likely to be living in a LTCF (0·019) and be classed as frail (0·014; table 3). However, when our analysis of the vaccine effectiveness of one dose of BNT162b2 was restricted to the period covered by the ChAdOx1 nCoV-19 analysis after the end of 2020, the observed adjusted estimate was 79·3% (95% CI 47·0–92·5; p=0·0014 *vs* 80·4% [36·4–94·5]; p=0·0083).

Discussion

As the rollout of available COVID-19 vaccines continues globally, there is an urgent need for real-world effectiveness data, particularly relating to severe disease in people aged at least 80 years—a high-risk group and a primary target for the UK vaccination programme. Furthermore, few people aged at least 80 years have been enrolled in randomised control trials of COVID-19 vaccines to date. All observational studies are subject to bias and more so 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 our work on this topic is ongoing and will deliver more granularity and precision over time, initial results are of immediate relevance to the formulation of and adjustments to current vaccination strategies in different countries using these vaccines.

The observed vaccine effectiveness of one dose of BNT162b2 against hospital admissions presented in this study estimates one dose effectiveness in adults aged at least 80 years on March 31, 2021 with extensive co-morbid disease. The phase 3 randomised controlled trial[2] of BNT162b2 enrolled few adults aged at least 80 years and evaluated the efficacy of two doses of BNT162b2 against symptomatic COVID-19; although the trial gave an indication of efficacy against admissions to hospital, the estimate was imprecise due to the scarcity of hospitalised participants. Thus, our findings of the vaccine effectiveness of a single dose of BNT162b2 in preventing hospital admission from COVID-19 infection in people aged at least 80 years, who were often frail and had many comorbidities, was encouragingly high.

By contrast with a whole population data-linkage study from Scotland, which reported effectiveness estimates of 60–85% for one dose of BNT162b2 against hospitalisation with COVID-19,[21] our study was restricted to the people aged at least 80 years and we adjusted for changes in exposure risk and groups targeted for vaccination over time. Our findings are consistent with a preprint by PHE, which reported a hazard ratio of 0·57 (0·58–0·67) for admissions to hospital (excluding accident and

emergency) when undergoing COVID-19 testing more than 14 days after the first dose of BNT162b2.[7] Similarly, the SIREN study reported a one-dose BNT162b2 vaccine effectiveness of 70% (95% CI 55–85) at 21 days in health-care workers.[22] SARI-Watch reported the effectiveness of BNT162b2 to be 57% (95% CI 48–63) after first dose in participants aged at least 80 years.[23] A case-control study from Israel found the estimated effectiveness of BNT162b2 against symptomatic disease in adults aged at least 70 years was 44% (95% CI 49–64) at 14–24 days after one dose and 64% (37–83) at 21–27 days after one dose.[3] In the same cohort, one dose of BNT162b2 had an estimated effectiveness against hospitalisation of 74% (95% CI 56–86) at 14–24 days after first dose and 78% (61–91%) at 21–27 days after first dose.[3] Other studies from Israel have reported that one dose of BNT162b2 has an effectiveness against COVID-19 laboratory-confirmed infection of 51% at 13–24 days after first dose,[24] or 75% at 15–28 days after first dose.[25] Taken together, our results and those of other studies suggest that, although substantial effectiveness can be expected after only one dose of BNT162b2, even in high-risk individuals, a second dose provides valuable additional protection.

There is a paucity of real-world data for the effectiveness of one dose of ChAdOx1 nCoV-19 in preventing SARS-CoV-2 infection in people of advanced age. This study reports estimated vaccine effectiveness of a single dose of ChAdOx1 nCoV-19 against hospitalisation in people aged at least 80 years, most of whom were frail and had comorbidities, using symptom onset to measure the time at which disease started post-vaccination. Data released from PHE suggest a hazard ratio for ChAdOx1 nCoV-19 of 0·63 (95% CI 0·41–0·97) in people aged at least 80 years when SARS-CoV-19 testing was undertaken more than 14 days after the first dose.[7] The results from this test-negative, case-control study show that a single dose of ChAdOx1 nCoV-19 induces a high level of protection against severe COVID-19 disease in a real-world patient group aged at least 80 years.

A pooled analysis of four randomised trials reported the one-dose ChAdOx1 nCoV-19 effectiveness against symptomatic disease from 22–90 days after first dose as 76·0% (95% CI 59·3–85·9).[5] Neutralising anti-spike IgG antibody levels after a single vaccine dose peaked at day 28 post-vaccination. However, participants who received only a single dose of ChAdOx1 nCoV-19 had a median age of 36·3 years (IQR 28·0–48·0), and were therefore much younger than our cohort.[4] Data released from Scotland in April, 2021, reported 74–94% effectiveness of one dose of ChAdOx1 nCoV-19 against admission to hospital in the entire population between January and mid-February, 2021.[21]

The point estimates for the one-dose effectiveness of each of the two vaccines 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 show several differences. The Pfizer BNT162b2 vaccine was introduced in the UK when numbers of cases were rising, but

	BNT162b2 (Pfizer; n=108)	ChAdOx1 nCoV-19 (Oxford–AstraZeneca; n=62)	p value
Age, median years (IQR)	86·4 (83·5–90·2)	87·5 (84·0–91·8)	0·29
Sex			
Female	44 (41%)	27 (43%)	0·75
Male	64 (59%)	35 (57%)	0·85
Long-term care facility resident	21 (19%)	23 (37%)	0·019
Ethnicity			
White British	93 (86%)	49 (79%)	0·33
Other	<5	<5	NA
Unknown	12 (11%)	11 (18%)	0·33
Smoking			
Current	47 (44%)	31 (50%)	0·51
Ex-smokers	<5	<5	>0·99
Comorbidity scores			
Rockwood clinical frailty score			
0–4	29 (27%)	6 (10%)	0·014
5–9	79 (73%)	56 (90%)	0·014
Charlson comorbidity index	5·0 (4·0–6·0)	5·5 (5·0–6·8)	0·36
Respiratory			
Any	73 (68%)	38 (61%)	0·51
Chronic obstructive pulmonary disease	18 (17%)	17 (27%)	0·14
Asthma	15 (14%)	7 (11%)	0·80
Other*	6 (6%)	6 (10%)	0·49
Cardiovascular			
Any	66 (61%)	36 (58%)	0·82
Ischaemic heart disease	23 (21%)	20 (32%)	0·16
Atrial fibrillation	32 (30%)	13 (21%)	0·29
Congestive cardiac failure	23 (21%)	12 (19%)	0·92
Diabetes			
Any	21 (19%)	12 (19%)	>0·99
Type 1	<5	<5	>0·99
Type 2	20 (19%)	12 (19%)	>0·99
Neurological			
Dementia	11 (10%)	9 (15%)	0·55
Cognitive Impairment	10 (9%)	6 (10%)	>0·99
Cerebrovascular accident	13 (12%)	10 (16%)	0·61
Transient ischaemic attack	6 (6%)	5 (8%)	0·75
Other neurological disease†	<5	<5	>0·99
Oncology			
Solid organ cancer	9 (8%)	6 (10%)	0·99
Haematological malignancy	<5	<5	>0·99
Renal disease‡			
Mild	35 (32%)	29 (47%)	0·09
Moderate or severe	5 (5%)	<5	0·55

Data are n (%) unless otherwise stated. To maintain patient confidentiality, data with fewer than five patients have been amended to <5. *Includes bronchiectasis, pulmonary fibrosis, and other chronic respiratory conditions. †Includes Parkinson's disease, Huntingdon's disease, and other chronic neurological conditions. ‡Mild is chronic kidney disease stage 1–3; moderate or severe is chronic kidney disease stage 4–5, end-stage renal failure, or dialysis dependence.

***Table* 3: Characteristics of individuals who received one dose of either BNT162b2 or ChAdOx1 nCoV-19**

were considerably lower than case numbers were in early January, when ChAdOx1 nCoV-19 vaccination started. Perhaps more importantly, a sensitivity analysis restricting the observation period for BNT162b2 to the same period over which ChAdOx1 nCoV-19 was studied, resulted in point estimates for the two vaccines that were almost identical (79·3% for BNT162b2 and 80·4% for ChAdOx1 nCoV-19). This finding suggests that people aged at least 80 years who received one dose of BNT162b2 in December, 2020, might have been at greater COVID-19 risk than individuals who received either vaccine in January, 2021. Thus, changes in vaccine deployment and hospital care during the study period might have biased results to some degree in the earliest weeks of the programme. Such changes could have included, but are not been limited to, improvements in the avoidance of vaccinating people already infected and, in some cases, symptomatic with COVID-19; 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. First, the BNT162b2 and ChAdOx1 nCoV-19 vaccines 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 health care does not limit vaccine availability, and vaccinated adults are less likely to be wealthier than unvaccinated adults than in fee-based or insurance-based health systems,[26] meaning that our study is not subject to the biases associated with fee-based or insurance-based health care. Second, by using a regression analysis that adjusted for week of symptom onset, we reduced the risk of bias attributable to any prioritisation that might have occurred in vaccination strategy or changes in background COVID-19 rates and, therefore, exposure to infection. Third, we also adjusted for socioeconomic status using index of multiple deprivations because this might affect an individual's likelihood of vaccine uptake, infection, and severe disease rates.[27] Fourth, we used the date of symptom onset to define the start of illness and provide a time estimate for infection after vaccination. We were, therefore, able to define the start of illness relative to both vaccine administration and hospitalisation accurately, without relying on the date of first positive COVID-19 test, eliminating bias or misclassification that could occur via the use of test date alone (which can vary widely). Finally, the observed ORs for both vaccines over the first 14 days after administration—when no protection was to be expected—were both close to 1 (although the confidence intervals were wide) suggesting that there was, at worst, only limited bias in these cohorts over the periods studied.

Our study has several limitations. First, we estimated vaccine effectiveness of one dose against COVID-19-related admission to hospitalisation and have not yet explored other secondary outcomes, including disease severity, length of hospital stay, and mortality. We expect to include effectiveness estimates against different circulating virus variants in the future.[28]

Second, we did not measure the effect of one dose in individuals who were not admitted to hospital with COVID-19, and there might be treatment bias where people of advanced age are not referred to hospital. This study provides vaccine effectiveness 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 to hospital or who were otherwise not referred to hospital were not included in this study. Patients with severe disease seen in general practice or accident and emergency might have been included in this analysis (via referral), 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 intervals from symptom onset to hospitalisation for vaccinated individuals.

Third, sampling and processing might have resulted both in false positive and negative PCR results, which could have rendered the effectiveness estimates imprecise to some degree with uncertain direction and size of any such biases.

Fourth, the study cohort was predominantly White and the effectiveness of these vaccines might differ 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.

Fifth, this analysis was done in one location on a small number of participants and, by necessity, over a short time period, which restricts the generalisability of the findings.

Sixth, we did not assess vaccine effectiveness against individual variants of SARS-CoV-2, 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. Finally, although we controlled 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 required to control for these potential confounders better.

In summary, the findings of our case-control analysis will help to guide strategy development for the use of BNT162b2 and ChAdOx1 nCOV-19 vaccines in clinical practice and should reassure policy makers of the high value of deploying these vaccines, and the importance of

administering two doses, in high-risk populations in whom incidence of severe disease and death from SARS-CoV-2 infection remains high.

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. AF provided oversight of the research. All authors had full access to all data in the study, had final responsibility for the decision to submit for publication, and were involved in the final manuscript preparation and its revisions before publication.

Declaration of interests

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 JCVI and is chair of WHO's European Technical Advisory Group of Experts on Immunization 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 COVID-19 vaccines including ChAdOx1 nCOV-19, Janssen, and Valneva vaccines. The other authors have no relevant conflicts of interest to declare.

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.

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