Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study

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Summary

Background The effectiveness of SARS-CoV-2 vaccines in older adults living in long-term care facilities is uncertain. We investigated the protective effect of the first dose of the Oxford-AstraZeneca non-replicating viral-vectored vaccine (ChAdOx1 nCoV-19; AZD1222) and the Pfizer-BioNTech mRNA-based vaccine (BNT162b2) in residents of long-term care facilities in terms of PCR-confirmed SARS-CoV-2 infection over time since vaccination.

Methods The VIVALDI study is a prospective cohort study that commenced recruitment on June 11, 2020, to investigate SARS-CoV-2 transmission, infection outcomes, and immunity in residents and staff in long-term care facilities in England that provide residential or nursing care for adults aged 65 years and older. In this cohort study, we included long-term care facility residents undergoing routine asymptomatic SARS-CoV-2 testing between Dec 8, 2020 (the date the vaccine was first deployed in a long-term care facility), and March 15, 2021, using national testing data linked within the COVID-19 Datastore. Using Cox proportional hazards regression, we estimated the relative hazard of PCR-positive infection at 0–6 days, 7–13 days, 14–20 days, 21–27 days, 28–34 days, 35–48 days, and 49 days and beyond after vaccination, comparing unvaccinated and vaccinated person-time from the same cohort of residents, adjusting for age, sex, previous infection, local SARS-CoV-2 incidence, long-term care facility bed capacity, and clustering by long-term care facility. We also compared mean PCR cycle threshold (Ct) values for positive swabs obtained before and after vaccination. The study is registered with ISRCTN, number 14447421.

Findings 10 412 care home residents aged 65 years and older from 310 LTCFs were included in this analysis. The median participant age was 86 years (IQR 80–91), 7247 (69·6%) of 10 412 residents were female, and 1155 residents (11·1%) had evidence of previous SARS-CoV-2 infection. 9160 (88·0%) residents received at least one vaccine dose, of whom 6138 (67·0%) received ChAdOx1 and 3022 (33·0%) received BNT162b2. Between Dec 8, 2020, and March 15, 2021, there were 36 352 PCR results in 670 628 person-days, and 1335 PCR-positive infections (713 in unvaccinated residents and 612 in vaccinated residents) were included. Adjusted hazard ratios (HRs) for PCR-positive infection relative to unvaccinated residents declined from 28 days after the first vaccine dose to 0·44 (95% CI 0·24–0·81) at 28–34 days and 0·38 (0·19–0·77) at 35–48 days. Similar effect sizes were seen for ChAdOx1 (adjusted HR 0·32, 95% CI 0·15–0·66) and BNT162b2 (0·35, 0·17–0·71) vaccines at 35–48 days. Mean PCR Ct values were higher for infections that occurred at least 28 days after vaccination than for those occurring before vaccination (31·3 [SD 8·7] in 107 PCR-positive tests *vs* 26·6 [6·6] in 552 PCR-positive tests; p<0·0001).

Interpretation Single-dose vaccination with BNT162b2 and ChAdOx1 vaccines provides substantial protection against infection in older adults from 4–7 weeks after vaccination and might reduce SARS-CoV-2 transmission. However, the risk of infection is not eliminated, highlighting the ongoing need for non-pharmaceutical interventions to prevent transmission in long-term care facilities.

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Introduction

The greatest effects of SARS-CoV-2 have been in residents of long-term care facilities, who represent a fraction of the population but account for a disproportionate number of SARS-CoV-2-related deaths in many countries, including the UK.[1] The UK has prioritised vaccination of residents and staff in long-term care facilities[2] to reduce the risk of COVID-19-related morbidity and mortality in this population, with the expectation that this will facilitate the relaxation of social restrictions.

Research in context

Evidence before this study

We searched MEDLINE and medRxiv for studies evaluating SARS-CoV-2 vaccine effectiveness in residents of long-term care facilities that were published in English between Jan 1, 2020, and March 11, 2021. We used variations of the search terms "COVID-19" AND "vaccine effectiveness" OR "vaccine efficacy" AND "care homes" OR "long term care facilities" OR "older people". We identified one preprint article concerning long-term care facilities in Denmark, which reported that a single dose of BNT162b2 (rINN tozinameran) was ineffective against SARS-CoV-2 infection in residents; however, participants received the second vaccine dose a median of 24 days after the first dose, which could be too soon to capture the protective effects of a single vaccine dose. Additionally, we identified two preprint reports of studies that evaluated vaccine effectiveness against symptomatic infection and admission to hospital among older adults in the community. The first of these preprints found 81% vaccine effectiveness against COVID-19-related admission to hospital at 28–34 days after a single dose of BNT162b2 or ChAdOx1 (AZD1222) in those aged 80 years and older. The second of these preprints found vaccine effectiveness against symptomatic infection of 60% at 28–34 days and 73% at 35 days and beyond after a single dose of ChAdOx1 in those aged 70 years and older. Although further reports from cohorts in long-term care facilities have become available, we identified no study that focused on the effectiveness of a single vaccine dose against infection among long-term care facility residents at more than 4 weeks after vaccination—a particularly important research question in the context of the UK policy decision to extend the dosing interval beyond 3 weeks.

Added value of this study

In this prospective cohort study in 10 412 residents aged 65 years and older from 310 long-term care facilities across England, we estimated vaccine effectiveness to be 56% (95% CI 19–76) at 28–34 days and 62% (23–81) at 35–48 days after a single dose of ChAdOx1 or BNT162b2. Our findings

suggest that the risk of SARS-CoV-2 infection is substantially reduced from 28 days after the first dose of either vaccine, and this effect is maintained up to at least 7 weeks after vaccination, with similar protection offered by both vaccine types. We also found that PCR cycle threshold values, which are negatively associated with the ability to isolate virus, were significantly higher in infections occurring at 28 days or longer after vaccination than in infections that occurred during the unvaccinated period, suggesting that vaccination might reduce onward transmission of SARS-CoV-2 from individuals with breakthrough infections. In addition to examining vaccine effectiveness in the context of an extended dosing interval and focusing on the frail and older long-term care facility resident population, our findings constitute some of the earliest real-world evidence on vaccine effectiveness against infection for ChAdOx1, in any age group. We can also infer that both vaccines are effective against the B.1.1.7 variant, because our analysis period coincided with the rapid emergence of B.1.1.7 in England during the second wave of the pandemic.

Implications of all the available evidence

Our findings add to the growing body of evidence on the protective effect of the BNT162b2 vaccines in residents in long-term care facilities and show the effectiveness of ChAdOx1 in this vulnerable population. Evaluating single-dose vaccine effectiveness has become increasingly important considering the extended dosing intervals that have been implemented across many countries to maximise vaccine coverage across high-risk groups. Further research is required to evaluate the effectiveness of the first vaccine dose at 8–12 weeks, as well as after the second dose, and to evaluate the long-term impact of vaccination on SARS-CoV-2 infection, transmission, and mortality in residents in long-term care facilities. Such research will inform policy decisions regarding the ongoing need for disease control measures in long-term care facilities, such as visitor restrictions, which continue to have a detrimental impact on the wellbeing of residents, their relatives, and staff.

Two vaccines have been deployed in long-term care facilities in England: the Oxford-AstraZeneca non-replicating viral-vectored vaccine (ChAdOx1 nCoV-19; AZD1222), licensed on Dec 30, 2020, and the Pfizer-BioNTech mRNA-based vaccine (BNT162b2; rINN tozinameran), licensed on Dec 2, 2020.[3] Both are spike protein-based vaccines that showed high efficacy (62·1–95·0%) against symptomatic infection in phase 3 clinical trials when following a two-dose schedule.[4,5] However, trials for both vaccines enrolled mostly young, healthy adults. Vaccine efficacy data from frail, older adults requiring long-term care are scarce because these individuals are routinely excluded from clinical studies and vaccine trials.[6] Consequently, trial estimates of vaccine efficacy might not be generalisable to long-term

care facility residents because of age-related differences in vaccine-induced immune responses.[7–9] Observational data from post-licensure studies in older adults are emerging,[10–12] and although a small number of preprint articles have reported on populations in long-term care facilities,[13–16] the study populations were exclusively vaccinated with BNT162b2 at the manufacturer-recommended dosing interval, and regular asymptomatic screening was rarely done.

Manufacturer-recommended dosing intervals for BNT162b2 and ChAdOx1 vaccines are 3 weeks and 4 weeks, respectively, although trial data indicate increased efficacy with an extended dosing interval for ChAdOx1.[17] On Dec 31, 2020, the UK Joint Committee on Vaccination and Immunisation advised that dosing

intervals could be extended up to 12 weeks to optimise first-dose coverage.[18] This decision was made in the context of rapidly increasing SARS-CoV-2 incidence, associated with the emergence of the highly transmissible B.1.1.7 variant and its subsequent spread within long-term care facilities from November, 2020.[19,20] This policy has made it increasingly important to understand the extent and duration of protection against infection afforded by the first dose of each vaccine, and whether single-dose vaccination has an effect on transmission.

We analysed data from our prospective observational cohort study to investigate the protective effect of the first dose of ChAdOx1 and BNT162b2 vaccines in residents of long-term care facilities aged 65 years and older, comparing the relative hazards of PCR-confirmed SARS-CoV-2 infection and mean PCR cycle threshold (Ct) values between vaccinated and unvaccinated residents by time since vaccination.

Methods

Study design and setting

The VIVALDI study is a prospective cohort study, which commenced recruitment on June 11, 2020, to investigate SARS-CoV-2 transmission, infection outcomes, and immunity in residents and staff in long-term care facilities in England that provide residential or nursing care for adults aged 65 years and older.[21] The study included care homes that were managed by for-profit and not-for-profit providers and independent long-term care facilities from all regions in England. Eligible long-term care facilities were identified by the care provider's senior management team or by the National Institute for Health Research Clinical Research Network.

Since July 6, 2020, all residents in long-term care facilities in England have been offered regular SARS-CoV-2 testing using PCR-based assays of naso-pharyngeal swab specimens.[22] Long-term care facility residents undergo monthly routine PCR testing and, if an outbreak is suspected, local public health teams organise PCR testing for all residents upon notification and 7 days later. Individuals who test positive are not retested for the following 90 days unless they develop new COVID-19 symptoms.[23] Symptom information is collected at the point of testing but its reliability is uncertain in this frail population.

Enrolled long-term care facilities continued to implement national guidelines regarding non-pharmaceutical interventions in care settings, including social distancing, isolation of symptomatic and confirmed cases, use of personal protective equipment by staff, visitor restrictions, and outbreak control measures, throughout the study period.[24] The study period coincided with a large second wave of the pandemic in England. Incidence of SARS-CoV-2 in England increased rapidly from 166·9 cases per 100 000 population on Dec 8, 2020, peaking at 680·6 per 100 000 population on Jan 4, 2021, followed by a gradual decline to 56·8 per 100 000 at the end of the study period on March 15, 2021. The second wave of SARS-CoV-2 transmission might have been driven in part by the emergence of the B.1.1.7 variant, which was initially identified in southeast England in October, 2020, and became the predominant strain nationally by the end of December, 2020.[19] Although vaccination commenced in December, 2020, in the UK, most first vaccinations in the study cohort occurred in January, 2021 (appendix p 2).

Residents were eligible for inclusion in the study if they had at least two PCR test results available at any time up to March 15, 2021, and at least one PCR result during the analysis period (Dec 8, 2020, to March 15, 2021). Residents entered the risk period on Dec 8, 2020, if they had at least one valid PCR result on or before that date or on the date of their first negative PCR test if they had no PCR results before Dec 8, 2020. Residents with a positive PCR result within 90 days before Dec 8, 2020, entered the risk period 90 days after their positive test. Residents exited the study at the earliest of the following events: positive PCR test, date of second vaccination, or last available PCR test.

Ethical approval for the study was obtained from the South Central—Hampshire B Research Ethics Committee (20/SC/0238). Consent was obtained from all individuals who donated a blood sample during the study; however, the legal basis to access data from staff and residents without informed consent was provided by the Control of Patient Information Regulations, which requires organisations to process confidential patient information for COVID-19 purposes (appendix p 4).

Data extraction and linkage

Data were extracted for the period of March 1, 2020, to March 15, 2021. We retrieved routine PCR testing data, including both positive and negative results, and any positive PCR results from hospital-based clinical testing, as well as age, sex, and long-term care facility location data from the COVID-19 Datastore, which was established as part of the UK's pandemic response. Void tests were excluded from the analysis. Where available, Ct values were retrieved directly from pillar 2 testing laboratories for positive PCR tests within the study period.

PCR results from the national testing programme were linked to specific residents using a pseudo-identifier, which is based on the individuals' unique UK National Health Service (NHS) number. The Care Quality Commission regulates all providers of health and social care in England. PCR results from the national testing programme were linked to specific care homes using the Care Quality Commission unique location identification (CQC-ID), making it possible to link residents to specific long-term care facilities. Residents with PCR tests linked to multiple CQC-IDs were assigned to the long-term care facility that corresponded to their most recent PCR test.

See **Online** for appendix

For the **COVID-19 Datastore** see https://data.england.nhs.uk/covid-19/

For more on the **Care Quality Commission** see https://www.cqc.org.uk/

For the **GOV.UK summary of daily COVID-19 data** see https://coronavirus.data.gov.uk/

Figure 1: Study flowchart

Flowchart contents:
42 454 individual records identified
→ 1458 duplicate records excluded
40 996 unique individuals
→ 5876 individuals with no PCR results excluded
35 120 individuals with one or more PCR results
→ 5621 individuals with only one PCR result excluded
29 499 individuals with two or more PCR results
→ 4928 individuals with no PCR results in the study period excluded
24 571 individuals with PCR results in the study period
→ 73 individuals with no time at risk in the study period excluded
24 498 individuals with time at risk in the study period
→ 13 717 individuals who were long-term care facility staff excluded
10 781 long-term care facility residents with time at risk in the study period
→ 360 long-term care facility residents aged <65 years excluded
10 421 eligible long-term care facility residents
→ 9 residents of one long-term care facility with no vaccine record linkage excluded
10 412 individuals in final analysis cohort

	Participants (n=10 412)
Age (years)	86 (80–91)
Sex	
Female	7247 (69·6%)
Male	3165 (30·4%)
Linked with single long-term care facility	10 271 (98·6%)
Evidence of previous infection	
Pre-vaccination N-antibody result available	864 (8·3%)
N-antibody positive pre-vaccination	194 (22·5%)
PCR-positive before the analysis period	1013 (9·7%)
Total with evidence of previous infection	1155 (11·1%)
PCR tests	
Total PCR results in at-risk period	36 352
Routine PCR tests	36 144 (99·4%)
Symptomatic at time of routine testing	246 (0·6%)
PCR results per person per month	1·6 (1·2–2·2)
PCR-positive events in analysis period	1335 (3·7%)
Routine PCR tests	1128 (84·5%)
Symptomatic at time of routine testing	84 (7·4%)
Vaccination	
First vaccine dose	9160 (88·0%)
ChAdOx1	6138 (67·0%)
BNT162b2	3022 (33·0%)
Second vaccine dose	897 (8·6%)
ChAdOx1	179 (20·0%)
BNT162b2	718 (80·0%)
Different first and second dose vaccine types	3 (0·3%)
Dose interval (days)	63 (55–65)

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

Table 1: **Characteristics of individual long-term care facility residents**
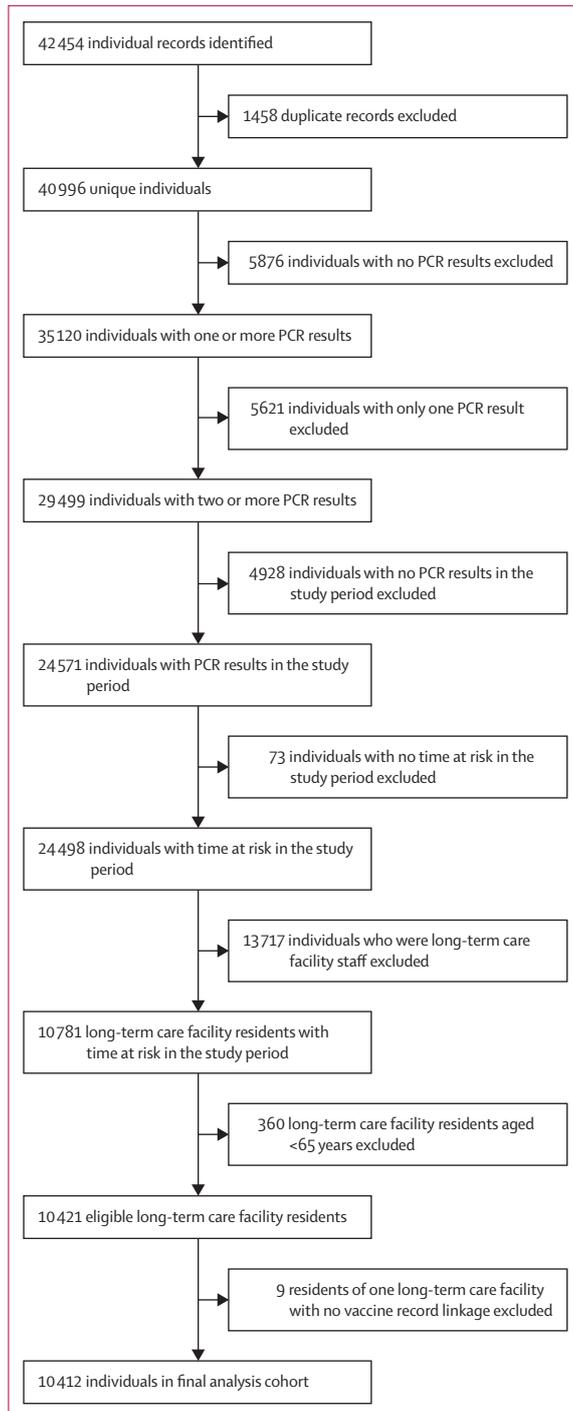
The NHS number-based pseudo-identifier was used to retrieve vaccination records (date, vaccine type, and dose number) from the National Immunisation Management Service (NIMS) and to link residents to antibody test results, both of which are held in the COVID-19 Datastore. All residents were eligible to participate in serum sampling to detect IgG antibodies to the nucleocapsid protein, subject to provision of valid, informed consent. A personal or nominated consultee was identified to act on behalf of residents who lacked the capacity to consent, and written informed consent was given by those who were able. As long-term care facility recruitment was ongoing, some facilities had not yet commenced serum sampling at the time of the analysis. Therefore, serological results were available for a subset of participants. We combined positive PCR results from before the analysis period and positive anti-nucleocapsid antibody results before vaccination into a binary variable for previous SARS-CoV-2 infection.

Estimates of the total number of beds (bed capacity) and weekly bed occupancy in each long-term care facility were retrieved from Capacity Tracker where possible, a national reporting tool that collates weekly operational data from long-term care facility managers. We sought the information directly from the facility managers

where it was not available through Capacity Tracker. England is divided into 343 local authorities, which are responsible for the delivery of community services, such as social care and education. Weekly SARS-CoV-2 incidence estimates at the local authority level, produced by the UK Department of Health and Social Care,[25] were used to derive the mean monthly incidence of SARS-CoV-2 in the area surrounding each long-term care facility. The data platform within the COVID-19 Datastore that was used to build the dataset used in this analysis was provided by Palantir Technologies UK under a general contract with the UK Government. The Palantir team worked under the instruction of the research team and only had access to pseudonymised data. Vaccination data from NIMS were validated against coverage estimates from long-term care facilities, where available. Long-term care facilities with no record of resident vaccination within NIMS were excluded from the analysis. The linked dataset was analysed in the University College London Data Safe Haven. A data privacy impact assessment was done for the VIVALDI study before the analysis.[26]

The mean Ct value for each PCR-positive test was calculated by taking the mean of the available Ct values from up to three gene targets (*N*, *ORF1ab*, and *S*) for each sample (appendix p 3).

Statistical analysis

We did an individual-level analysis of the risk of PCR-confirmed SARS-CoV-2 infection by vaccination status among residents aged 65 years and older from long-term care facilities enrolled in the VIVALDI study. The analysis period started from the date of first vaccination in the cohort (Dec 8, 2020) and ended at the date of last data extraction (March 15, 2021). The sample size for the VIVALDI study was based on the precision of estimates for antibody prevalence;[21] therefore, a-priori sample size calculations were not done for this analysis.

We used Cox proportional hazards models to derive adjusted hazard ratios (HRs) for the risk of a first PCR-positive test in the study period. Vaccination status was included as a time-varying covariate in the model, with the unvaccinated exposure group compared against exposure groups at 0–6 days, 7–13 days, 14–20 days, 21–27 days, 28–34 days, 35–48 days, and 49 or more days after the first dose of either vaccine. The same cohort contributed person-time at risk to unvaccinated and vaccinated exposure categories, with most individuals starting in the unvaccinated state and sequentially transitioning through vaccinated exposure states until the outcome of interest or being censored at the point of second vaccination or their last available PCR result. The baseline hazard was defined over calendar time. We adjusted for sex (as a binary variable), age (as a cubic spline term), evidence of previous SARS-CoV-2 infection (as a binary variable), long-term care facility bed capacity (as a linear term), and monthly SARS-CoV-2 incidence

	Long-term care facilities (n=310)
For-profit chain	228 (73·5%)
Number of included residents	7456/10 412 (71·6%)
Not-for-profit chain	72 (23·2%)
Number of included residents	2537/10 412 (24·4%)
Independent	10 (3·2%)
Number of included residents	419/10 412 (4·0%)
Total bed capacity	48 (40–63)
Occupied beds	38·5 (30·0–50·2)
Occupancy	82·5% (71·7–90·5)
Vaccinated residents	90·9% (85·7–95·7)
Most (>75%) residents vaccinated with ChAdOx1	203 (65·5%)
Total bed capacity	47 (38–61)
Occupied beds	37 (28–48)
Date by which >75% of long-term care facilities had started vaccination	Jan 19, 2021
Date by which >75% of long-term care facilities had completed >75% of vaccinations	Jan 21, 2021
Days taken to complete >75% of vaccinations	1 (1–2)
Most (>75%) residents vaccinated with BNT162b2	99 (31·9%)
Total bed capacity	51 (42–64)
Occupied beds	41 (32–54)
Date by which >75% of long-term care facilities had started vaccination	Jan 7, 2021
Date by which >75% of long-term care facilities had completed >75% of vaccinations	Jan 8, 2021
Days taken to complete >75% of vaccinations	1 (1–1)

Data are n (%), n/N (%), or median (IQR), unless otherwise indicated.

Table 2: Characteristics of long-term care facilities included in the analysis

for the local authority in which the long-term care facility was located (as a linear term). 95% CIs were calculated using robust SEs to account for dependence of infection events within long-term care facilities.

In secondary analyses, we explored vaccine effects stratified by type of vaccine (ChAdOx1 and BNT162b2) and by evidence of previous SARS-CoV-2 infection. Our stratified analyses were done by including an interaction term between the time-varying exposure status and the stratifying factor. We did a sensitivity analysis that excluded individuals who were never vaccinated despite having a PCR test more than 30 days after the date of first vaccination in their long-term care facility to account for potential bias from systemic differences in clinical or other features of this group.

We calculated vaccine effectiveness estimates as $100 \times (1 - \text{adjusted HR})$ and 95% CIs for vaccine effectiveness estimates as $100 \times (1 - \text{upper or lower bounds of 95% CI for adjusted HR})$. We used two-tailed t tests to estimate the difference in mean Ct values between unvaccinated and vaccinated groups. We also did a sensitivity analysis that limited comparison of Ct values to those obtained from the single most common assay type.

	Person-days at risk	PCR tests	PCR testing rate per 1000 person-days	Infection events	Infection rate per 10 000 person-days	Adjusted HR (95% CI)	p value
Unvaccinated	338 003	15 392	45·54	723	21·39	1 (ref)	..
0–6 days	47 591	2482	52·15	105	22·06	0·64 (0·38–1·06)	0·083
7–13 days	53 511	3189	59·60	139	25·98	0·83 (0·54–1·28)	0·404
14–20 days	50 362	2462	48·89	132	26·21	0·96 (0·57–1·60)	0·866
21–27 days	47 514	2478	52·15	95	19·99	0·92 (0·53–1·59)	0·762
28–34 days	43 136	2078	48·17	42	9·74	0·44 (0·24–0·81)	0·0087
35–48 days	63 012	4681	74·29	59	9·36	0·38 (0·19–0·77)	0·0069
≥49 days	27 499	3590	130·55	40	14·55	0·49 (0·20–1·17)	0·108
Overall	670 628	36 352	54·21	1335	19·91	..	..

Adjusted HRs were estimated using Cox proportional hazards regression according to days since the first vaccine dose; the comparator was the unvaccinated group. HRs are adjusted for age, sex, local monthly infection incidence, and long-term care facility bed capacity. 95% CIs were calculated using robust standard errors for long-term care facility-level effects. HR=hazard ratio.

Table 3: Infection rates and adjusted HRs for PCR-positive infection after the first dose of either vaccine, by days since vaccination (primary analysis)
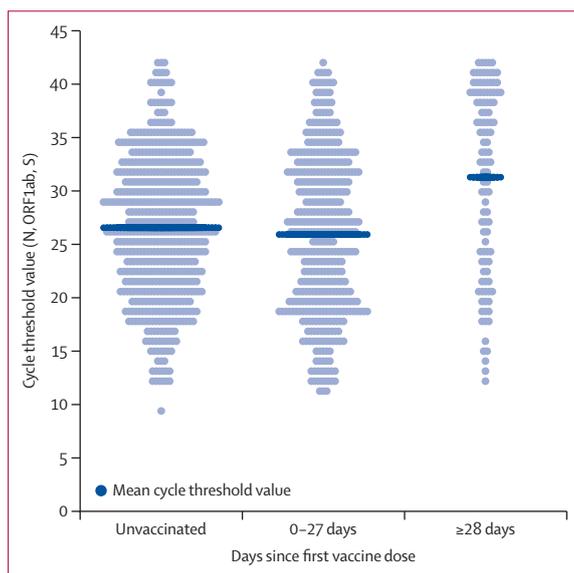

Figure 2: Cycle threshold values for PCR-positive tests, by exposure category

All analyses were prespecified in a statistical analysis plan and done in Stata version 16.0. The study is registered with ISRCTN, number 14447421.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
10 412 residents aged 65 years and older from 310 long-term care facilities were included in this analysis (figure 1; tables 1, 2). The median participant age was 86 years (IQR 80–91), 7247 (69·6%) of 10 412 residents were female, and 1155 residents (11·1%) had evidence of previous SARS-CoV-2 infection. 9160 (88·0%) residents received at least one vaccine dose, of whom 6138 (67·0%) received ChAdOx1 and 3022 (33·0%) received BNT162b2. 897 (8·6%) participants received a second vaccine dose, and the median dose interval was 63 days (IQR 55–65).

Data were available from 228 for-profit and 72 not-for-profit chain providers and ten independent facilities (table 2). Most included long-term care facilities had commenced resident vaccinations by Jan 16, 2021, and completed most of these within 2 days. Long-term care facilities that mainly used ChAdOx1 tended to be slightly smaller and started vaccinations slightly later than facilities that mainly used BNT162b.

Between Dec 8, 2020, and March 15, 2021, there were 36 352 PCR results in 670 628 person-days (54·2 PCR tests per 1000 person-days; table 3), and 1335 PCR-positive infections (713 in unvaccinated and 612 in vaccinated residents) were included. Most PCR results were completed as part of routine testing. The crude infection rate per 10 000 person-days at risk was 19·91 overall and 21·39 in the unvaccinated group (table 3). In vaccinated residents, the infection rate decreased to 9·74 per 10 000 person-days at 28–34 days after vaccination and 9·36 per 10 000 person-days at 35–48 days after vaccination.

In Cox regression analyses, we found no significant reduction in hazards of PCR-positive infection until 28–34 days after vaccination (adjusted HR 0·44, 95% CI 0·24–0·81; table 3). At 35–48 days, the adjusted HR was similar to that at 28–34 days at 0·38 (95% CI 0·19–0·77), equating to a vaccine effectiveness of 62% (95% CI 23–81). At 49 or more days, the estimates were much less precise and no longer significantly different compared with the unvaccinated group (adjusted HR 0·49, 95% CI 0·20–1·17). In this adjusted model, previous infection was strongly associated with a reduced hazard of subsequent infection (adjusted HR 0·19, 0·12–0·30).

Ct values were available for 1070 (80·1%) of 1335 positive PCR tests, from 13 laboratories using six different validated assays (appendix p 3). The mean Ct value of

	ChAdOx1					BNT162b2				
	Person-days at risk	Infection events	Infection rate per 10 000 person-days	Adjusted HR (95% CI)	p value	Person-days at risk	Infection events	Infection rate per 10 000 person-days	Adjusted HR (95% CI)	p value
Unvaccinated	338 003	723	21·39	1 (ref)	..	..	..	..	1 (ref)	..
0–6 days	30 823	61	19·79	0·51 (0·26–0·99)	0·045	16 768	44	26·24	0·84 (0·39–1·81)	0·663
7–13 days	34 598	66	19·08	0·58 (0·35–0·96)	0·035	18 913	73	38·60	1·11 (0·65–1·88)	0·700
14–20 days	32 672	82	25·10	0·95 (0·50–1·84)	0·889	17 690	50	28·26	0·77 (0·37–1·58)	0·473
21–27 days	30 640	50	16·32	0·73 (0·37–1·44)	0·358	16 874	45	26·67	0·94 (0·50–1·79)	0·859
28–34 days	27 041	23	8·51	0·33 (0·16–0·68)	0·0025	16 095	19	11·80	0·47 (0·20–1·06)	0·070
35–48 days	34 705	36	10·37	0·32 (0·15–0·66)	0·0023	28 307	23	8·13	0·35 (0·17–0·71)	0·0038
≥49 days	7421	16	21·56	0·64 (0·26–1·56)	0·329	20 078	24	11·95	0·38 (0·15–0·93)	0·034
Total (vaccine type)	197 900	334	16·88	..	..	134 725	278	20·63	..	..

Adjusted HRs were estimated using Cox proportional hazards regression according to days since the first vaccine dose for each vaccine type (ChAdOx1 and BNT162b2). The comparator was the unvaccinated group. HRs were adjusted for age, sex, local monthly infection incidence, and long-term care facility bed capacity. 95% CIs were calculated using robust standard errors for long-term care facility-level effects. HR=hazard ratio.

Table 4: Infection rates and adjusted HRs for PCR-confirmed infection after the first dose of vaccine, by vaccine type and days since vaccination (secondary analysis)

552 PCR-positive tests from the unvaccinated group was 26·6 (SD 6·6). Although we observed no evidence of a difference when comparing the mean Ct values from the unvaccinated group with that of the 411 PCR-positive tests from 0–27 days after vaccination (mean Ct 25·9 [SD 7·4]; p=0·158), the mean Ct value of the 107 PCR-positive tests occurring 28 or more days after vaccination was significantly higher (31·3 [8·7]; p<0·0001; figure 2; appendix p 5). A sensitivity analysis limited to a single assay with the most available results gave the same finding (appendix p 5).

The adjusted HRs for infection after ChAdOx1 vaccination were 0·33 (95% CI 0·16–0·68) at 28–34 days after vaccination and 0·32 (0·15–0·66) at 35–48 days after vaccination. The adjusted HRs for infection after BNT162b2 vaccination were 0·47 (0·20–1·06) at 28–34 days after vaccination and 0·35 (0·17–0·71) at 35–48 days after vaccination (table 4; appendix p 6). These estimates equated to vaccine effectiveness of 68% (95% CI 34–85) and 65% (29–83) at 35–48 days for ChAdOx1 and BNT162b2, respectively. We found evidence to suggest that protective effects remained beyond 7 weeks for BNT162b2 but not for ChAdOx1. Additionally, we observed a reduced risk of PCR-positive infection in the early period after vaccination (0–13 days) in long-term care facility residents who received ChAdOx1 but not in those who received BNT162b2.

In long-term care facility residents with no evidence of previous infection, the protective effect of vaccination was similar to that observed in the main analysis (adjusted HR 0·36, 95% CI 0·18–0·73 at 35–48 days; appendix p 7). When compared with unvaccinated residents with no previous SARS-CoV-2 infection, unvaccinated residents with previous infection had a significantly lower hazard of infection (adjusted HR 0·12, 95% CI 0·04–0·35). Among long-term care facility residents with previous SARS-CoV-2 infection, we found no evidence to suggest that a single dose of vaccine further reduced the risk of PCR-positive infections beyond previous infection alone at any timepoint (appendix p 8). 439 (12·0%) of 1252 never-vaccinated residents had at least one PCR result available more than 30 days after the date of first vaccination in their long-term care facility (appendix p 9), indicating that they remained unvaccinated while other residents were being vaccinated. Removing this group from the analysis reduced the adjusted HRs for infection to 0·29 (95% CI 0·13–0·63) at 28–34 days after the first dose compared with the unvaccinated group (appendix p 10), equating to a vaccine effectiveness of 71% (95% CI 37–87).

Discussion

In this large cohort study in more than 10 400 long-term care facility residents across England, single-dose vaccination with ChAdOx1 or BNT162b2 was associated with a substantially reduced risk of PCR-positive SARS-CoV-2 infection from 28 days, which is slightly later than onset of protection in the wider population (21 days),[12] and this effect was maintained for at least 7 weeks. We estimated vaccine effectiveness to be 56% (95% CI 19–76) at 28–34 days and 62% (23–81) at 35–48 days. Beyond this time, there was insufficient evidence for a protective effect when looking at both vaccines combined; however, data for BNT162b2, for which there was more person-time at risk available than for ChAdOx1, indicate that a protective effect was maintained beyond 7 weeks. We have only evaluated the effect of the first dose of each vaccine, but our findings constitute some of the earliest evidence on real-world effectiveness of the ChAdOx1 vaccine and of COVID-19 vaccines in long-term care facility residents. In addition to the existing trial and observational evidence on vaccine effectiveness against symptomatic disease, we show that vaccination reduces the total number of infections (asymptomatic and symptomatic) in older adults, and thus overall

transmission. An effect of vaccination on transmissibility is further supported by our finding of higher Ct values in infections occurring after vaccination, which are in line with those from large Israeli and UK cohorts,[12,27] implying that residents with post-vaccination breakthrough infections have lower potential for transmission than unvaccinated residents with infection.

Although the evidence on single-dose immunogenicity of BNT162b2 in older adults is mixed,[28–30] pooled data from four ChAdOx1 trials, including over 950 participants aged 70 years and older, indicated vaccine effectiveness of 63·9% (95% CI 46–75·9) against all infection at 22–90 days after a single dose,[17] which is in line with our findings. Our estimates of vaccine effectiveness against all infection are not dissimilar to those from phase 3 efficacy testing of the single-dose Ad26.COV2.S vaccine (Janssen), which was 67·9% (95% CI 38·2–82·8) effective against symptomatic COVID-19 at 28 days or more after vaccination in those aged 60 years and older.[31] This finding suggests any single-dose regimen is likely to provide similar levels of protection from 4 weeks. Although we found no additional benefit of vaccination in residents with previous natural infection, it remains important to examine the additional benefits provided to older adults by a second dose of vaccine, particularly in the context of new variants of concern, for which immunological data suggest the importance of a second inoculation.[32–34] Data from a Danish observational study in long-term care facility residents suggest that a single dose of BNT162b2 is ineffective in preventing infection;[13] however, participants received the second vaccine dose a median of 24 days after the first dose, which, based on our findings, is probably too short a period to capture the protective effects of a single vaccine dose. Two large Spanish studies in long-term care facility residents reported similar single-dose BNT162b2 vaccine effectiveness estimates to those reported here; however, these studies have limitations of shorter dosing intervals than used in the UK setting and little or no routine asymptomatic screening.[15,16]

We observed reduced hazards of infection in the immediate post-vaccination period (0–13 days) for ChAdOx1, which cannot be attributed to protective effects of the vaccine but might be because recently vaccinated long-term care facilities were less likely to have ongoing outbreaks of infection. Guidance on risk assessment-based deferral of vaccination in long-term care facilities with active outbreaks was introduced at the end of December, 2020,[35] and is likely to have disproportionately affected facilities predominantly using ChAdOx1, which was deployed later than BNT162b2. A similar effect has been observed following single-dose vaccination in health-care workers,[36] which was attributed to vaccine deferral due to COVID-19 illness. The effect of vaccination deferral on our estimates of vaccine effectiveness could not be ascertained because deferral decisions were not routinely recorded and are likely to have varied between settings.

We identified 439 individuals in our cohort who remained unvaccinated despite vaccine rollout within their long-term care facility. At least a subset of these individuals might have been receiving end-of-life care, but this cannot be confirmed without accessing primary care records, which were unavailable for this study. These residents had substantially lower infection rates than the wider unvaccinated group, which could be attributable to a lower risk of exposure in this group—for example, due to fewer external visitors and reduced interaction with other residents and staff. Sensitivity analysis excluding this group increased estimates of vaccine effectiveness to 76% (95% CI 37–91) at 35–48 days after vaccination.

A major strength of our analysis is that we could access high-quality, routinely collected data for a large, well-defined cohort of long-term care facility residents who were tested regularly for SARS-CoV-2 throughout follow-up. This access allowed us to estimate the effect of vaccination on all SARS-CoV-2 infections, by contrast with trials and most observational studies, which have focused on symptomatic infections. The analysis period coincided with the second wave of the pandemic, making it possible to estimate vaccine effectiveness against infections in the context of rapid emergence of the highly transmissible B.1.1.7 variant. Our cohort included a range of long-term care facility types, therefore we expect these findings to be generalisable across long-term care facility resident populations. Regarding limitations, as vaccines were rolled out rapidly in long-term care facilities in England and most resident vaccinations were completed over 1–2 days, we did not attempt to quantify indirect vaccine effects attributable to herd immunity. Staff and resident vaccinations took place concurrently, and the reliability of staff vaccination data were uncertain, so we did not adjust for staff vaccine coverage at the long-term care facility level in this analysis. We were also unable to assess the proportion of long-term care facilities that deferred vaccination because of COVID-19 outbreaks. Although it is likely that we have underestimated previous infection because of low rates of PCR testing in the first wave of the pandemic, as previous infection appears highly protective against reinfection,[37,38] we would expect this to attenuate our vaccine effectiveness estimates. We observed a lower PCR testing rate in the unvaccinated exposure category, and higher PCR testing rates at 35–48 days and 49 days and beyond after vaccination, than in earlier post-vaccination exposure categories. Although the reasons for these disparities are unclear, we would expect them to attenuate vaccine effectiveness estimates. The precision of vaccine effectiveness estimates at 49 days and beyond was reduced because of less person-time at risk in this exposure category than in other exposure categories. We considered Ct values, which correlate with the ability to isolate virus,[39] to be indicative of infectivity.[40] Although it is challenging to compare Ct values across different assays, all results targeted the same genes (*N, ORF1ab, S*),

and similar findings were obtained in a sensitivity analysis based on a single assay. Our analysis was restricted by absence of data on underlying conditions and frailty status of individual residents, and by scarcity of reliable symptom data, which precluded analysis of vaccine effectiveness against symptomatic infections, as well as reporting on vaccine safety. Future analyses should examine protection against infections caused by other emerging variants of concern and consider outcomes such as hospital admission and mortality, although treatment escalation decisions in the context of end-of-life care are likely to affect vaccination and COVID-19 outcomes.

In conclusion, single-dose vaccination with either ChAdOx1 or BNT162b reduces the risk of SARS-CoV-2 in older residents in long-term care facilities. Our findings suggest that vaccination also has an effect on SARS-CoV-2 transmissibility by reducing the total number of infections in residents, as well as their infectivity. The protective effect of a single dose of vaccination is evident from 4 weeks to at least 7 weeks after vaccination, which provides some evidence to support extension of the dose interval beyond 3 weeks, in line with UK policy. However, even beyond 4 weeks, a single vaccine dose does not eliminate infection risk, highlighting the continued importance of non-pharmaceutical measures to control transmission within long-term care facilities. Further work is required to evaluate the effectiveness of the second dose of the vaccine, and the effect of vaccination on transmission. This knowledge will be critical to inform policy decisions regarding revaccination schedules in this vulnerable population and the disease control measures needed in the short, medium, and long term to protect long-term care facilities from future waves of SARS-CoV-2 infection.

Contributors
LS, AC, JLB, MS, AH, MK, and SS conceived the study. AC, TP, MS, and LS devised the statistical methodology. MS, MK, and TP did the formal analysis. MK, BA, CF, and AI-S were project administrators. MK and DD curated and validated the data. BA, MK, and MS did the literature review. LS, AH, and AC acquired the funding. MS, LS, and MK wrote the original draft of the manuscript. All authors reviewed and edited the manuscript. MS, TP, AC, LS, and MK had full access to the data in the study. LS and AC have shared responsibility for the decision to submit for publication.

Declaration of interests
LS reports grants from the UK Department of Health and Social Care during the conduct of the study and is a member of the Social Care Working Group, which reports to the Scientific Advisory Group for Emergencies. AH is a member of the New and Emerging Respiratory Virus Threats Advisory Group at the UK Department of Health. DD is an employee of Palantir Technologies UK, which provided the data platform that was used for this study under a general contract with the UK Government (DHSC/NHS England and Improvement). All other authors declare no competing interests.

Data sharing
De-identified test results and some metadata will be made available for use by researchers in future studies, subject to appropriate research ethical approvals being obtained, once recruitment into the VIVALDI cohort has been completed. These datasets will be accessible via the Health Data Research UK Gateway.

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