Effects of BNT162b2 mRNA vaccine on Covid-19 infection and hospitalisation among older people: matched case control study for England

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Abstract

Background

The BNT162b2 mRNA vaccine has been shown to be effective at preventing serious Covid-19 events in clinical trials. There is less evidence on effectiveness in real-world settings, especially for older people. The rapid roll-out of the NHS vaccination programme in England based on age thresholds offers an opportunity to make unbiased comparisons of outcomes between vaccinated and unvaccinated populations.

Methods and Findings

We matched older (aged 80-83 years) vaccine recipients with younger (aged 76-79 years) persons not yet eligible to receive the vaccine on gender, area of residence, area deprivation, health status, living arrangements, acute illness, and history of seasonal flu vaccination. We also adjusted for the over-representation of Covid-19 positive individuals in the control population because eligibility for vaccination required no Covid-19 symptoms in the previous two weeks. The study population included 170,226 individuals between the ages of 80 and 83 years from community settings outside care homes who received one dose of BNT162b2 mRNA between the 15th and 20th December 2020 and were scheduled a second dose 21 days later.

We found emergency hospital admissions were 51.0% (95% confidence interval: 19.9% to 69.5%) lower and positive Covid-19 tests were 55.2% (40.8% to 66.8%) lower for vaccinated individuals compared to matched controls 21 to 27 days after first vaccination. Emergency admissions were 75.6% (52.8% to 87.6%) lower and positive Covid-19 tests were 70.1% (55.1% to 80.1%) lower 35 to 41 days after first vaccination when 79% of participants had received a second dose within 26 days of their first dose.

Conclusions

Receipt of the BNT162b2 mRNA vaccine is effective at reducing Covid-19 hospitalisations and infections. The nationwide vaccination of older adults in England with the BNT162b2 mRNA vaccine reduced the burden of Covid-19.

Introduction

Several vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have been demonstrated to be safe and highly effective in phase 3 randomised clinical trials, with efficacy estimates for prevention of symptomatic disease ranging from 62% to 95%.[1–4] However, it is also important to examine their effectiveness when deployed in mass vaccination campaigns across diverse populations, where trial exclusion criteria do not apply and where deviations from dosing and handling protocols may occur.

Early evidence from an observational study of mass vaccination using the BNT162b2 mRNA Covid-19 vaccine in Israel estimated real-world effectiveness consistent with reported trial efficacy.[3,5] This indirectly provided evidence that vaccine effectiveness was maintained against the more transmissible B.1.1.7. variant,[5,6] which was widespread in the population during the study period. Vaccine effectiveness estimates were consistent across age groups, though were slightly lower amongst people with multiple coexisting health conditions.[5] Similarly, estimates from Scotland[7] and England[8] provide further early evidence of effectiveness. However, such observational, non-randomised studies may be biased by systematic differences between intervention and control groups and between those receiving the intervention at different points in time. The remarkable speed of Covid-19 vaccination rollouts[5,7,8] and specific prioritisation of vulnerable groups[9] heighten the risk of these biases, as acknowledged in existing studies.[5,7,8]

We exploit age-based eligibility phasing in the early stages of the nationwide NHS population vaccination programme in England to estimate the real-world effectiveness of the BNT162b2 mRNA vaccine. We match vaccinated persons aged 80 to 83 years to younger persons who did not become eligible for the vaccine until three weeks later and compare their rates of Covid-19 infection and hospitalisation over the 45 days following the date of their first dose. It is particularly important to assess real-world vaccine effectiveness in this older population group, because severe Covid-19 is strongly age-associated[10] and adaptive immune responses decline with age.[11]

Methods

Data

MW and JH obtained population-wide person-level data for England, including vaccination details (date, type and dose), SARS-CoV-2 tests (date, result), age, gender, area of residence, use of hospital services and dates of death. For data sources, linkage methods and access, see Appendix 1. The study population was defined at mid-November 2020. Data were extracted on 9th February 2021 and include complete records to 3rd February 2021.

Study design

Concurrent with the vaccination programme, COVID-19 (B.1.1.7. variant) incidence in England varied widely, as the B.1.1.7. variant spread through the population[6] and a national lockdown was implemented.

The first phase of the NHS England vaccination programme targeted: (1) front-line health and social care workers, (2) older care home residents and their carers, and (3) people aged 80 years and over[9]. Differences in risks of exposure and outcome within the first two groups are not effectively measured in administrative datasets. We focused on 171,931 individuals aged 80-83 years not living in care homes

that received their first dose between 15ᵗʰ and 20ᵗʰ December 2020, of whom 78.8% received a second dose within 26 days.

We compared vaccinated cases to people aged 72-79 years who became eligible for vaccination later. The speed of vaccination rollout meant many of these received a first vaccine dose during the follow-up period (see Figure 1). We matched vaccinated cases to suitable controls separately for each day of the follow-up period, excluding as controls individuals vaccinated more than two weeks before the day for which outcomes were being compared.

Figure 1. Numbers of people in England who received their first COVID-19 vaccination dose between the 8th December 2020 and the 3rd February 2021 by age group. The cumulative totals are relative to estimates of eligible population based on extracts from the National Health Application and Infrastructure Services (NHAIS) system as of the 15th November 2020. Prior to the 4ᵗʰ January 2021 all individuals received the BNT162b2 mRNA vaccine, after which individuals were vaccinated with either the BNT162b2 mRNA or ChAdOx1 adenovirus vector vaccines.
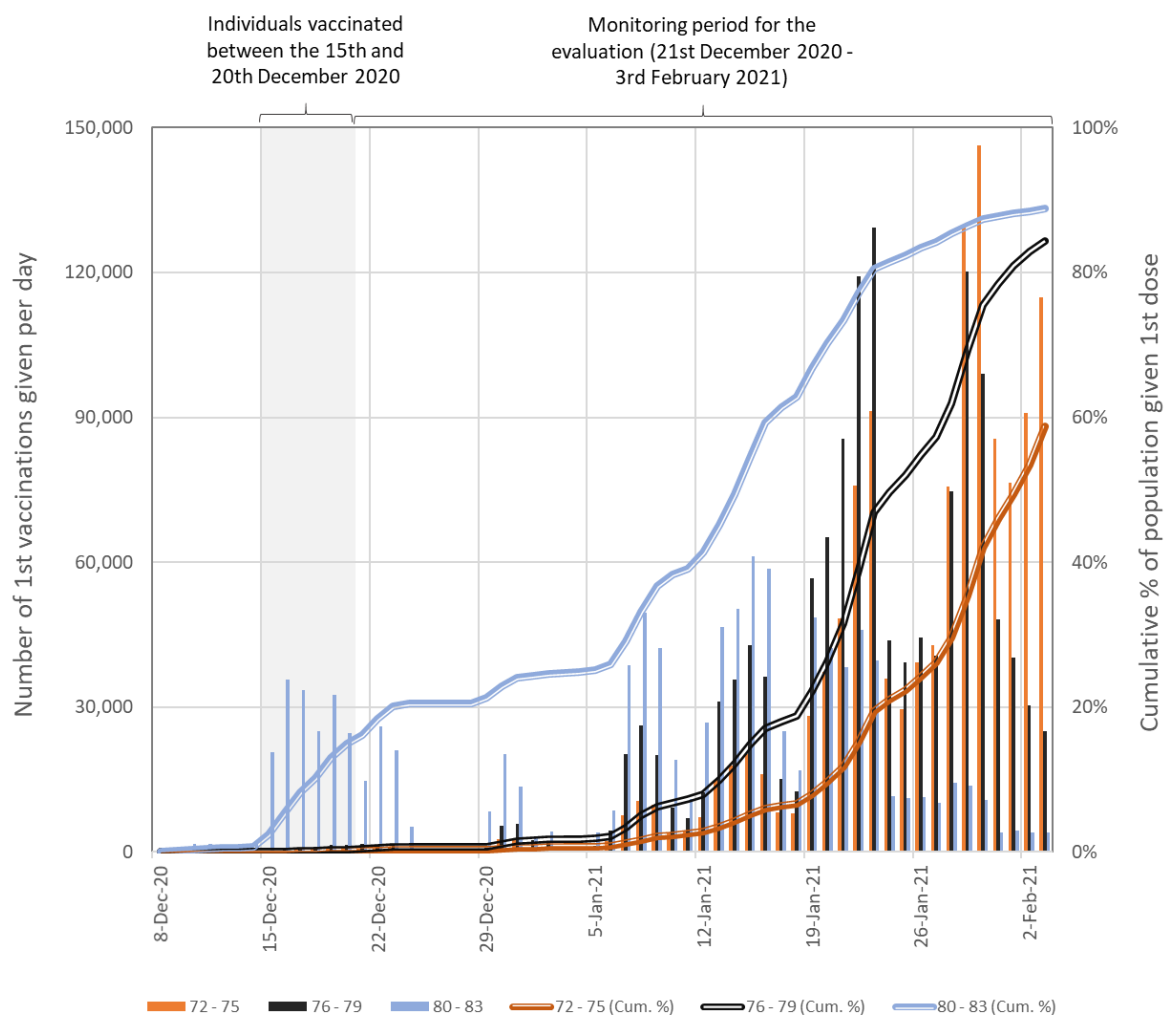
As individuals should not have had a COVID-19 infection in the two weeks prior to vaccination, the control group contains a progressively higher proportion of people who test positive for COVID-19. This selection process biases the rate of positive tests in the control group upwards and would artificially inflate estimated vaccine effectiveness. To correct for this bias, we sequentially adjusted event rates in the intervention and control groups so that they remained consistent in the first 11 days of follow-up, regardless of the date by which the control group could not (yet) have been vaccinated. Details of the adjustment method are provided in Appendix 2.

To explore adjustment robustness and the sensitivity of the results to the age group used for the controls, we compared the older age group to two different younger age groups. First, we matched vaccinated individuals aged 80-81 to controls aged 76-77, and vaccinated individuals aged 82-83 to controls aged 78-79. Second, we matched vaccinated individuals aged 80-81 to controls aged 72-73, and vaccinated individuals aged 82-83 to controls aged 74-75. The younger control group is less similar in age but unexposed to the vaccine for longer and therefore less prone to selection bias.

We examined rates per 100,000 people for three outcomes: SARS-CoV-2 infection and Covid-19 related hospital attendances and hospitalisations. Infection was recorded by specimen date of SARS-CoV-2 positive polymerase-chain-reaction (PCR) test results from health care facilities (called Pillar 1 testing) or community testing (Pillar 2). Covid-19 related A&E attendances were measured using diagnosis information from emergency department records combined with linked positive Covid-19 test results from 14 days before to 6 days after the attendance (see Appendix 3). Covid-19 related hospital admissions were measured using admitted patient care spell records available on discharge, limited to lengths of stay of 42 days or less. The required information is available for 95% of all emergency department attendances and 93% of all emergency admissions.

Matching and statistical analysis

Isolating the impact of vaccination requires a study design that accounts for temporal changes in infection rates, for which we used 1:1 exact matching[12] to account for several factors associated with exposure and outcomes: gender; area of residence;[13] small area deprivation;[14] ethnic group; health status; living arrangements; seasonal influenza vaccine history since April 2020; and emergency hospital stays in the previous two months. We excluded 1,705 (1.0%) individuals with prior Covid-19 history to avoid likely pre-existing immunity.[15,16] We excluded individuals from the control group if they were living in care homes or were not alive on the 15th of December 2020. We dropped matched pairs where either individual was in hospital on the vaccination date or the pair lived at the same property (see Figure 2).

We matched vaccinated individuals to unique controls without replacement. We assigned a control randomly where multiple matches were available for a vaccinated individual. We repeated the matching process five times with different random number seeds to create five matched populations. We bootstrapped 100 samples with replacement from each of these five matched populations and obtained confidence intervals using percentile values from the 500 samples.

We used the STROBE cohort checklist when writing our report.[17]

Results

Study population

Of the total 1,685,530 individuals aged 80-83, 170,226 were not residents of care homes, had no prior history of Covid-19, and received a first dose of the BNT162b2 mRNA vaccine between 15th-20th December 2020, so were eligible for inclusion in the study (Figure 2). Of these, we exact-matched 131,236 (77.1%) to control individuals aged 76-79 who were not yet eligible for vaccination (Figures 1&2). The requirement for an exact match generated a matched study population with lower proportions of individuals who were frail or clinically extremely vulnerable, from minority ethnic groups, or from socially-deprived areas compared to the full study population (Table 1 & Appendix 4).

Figure 2. Flow diagram of the study population with eligibility criteria, exclusions and matching methodology.

53,064,537 individuals aged 18 years and over registered with a GP in England as of 15th November 2020

1,663,392 individuals aged 80 to 83 years at the start of the vaccination period

1,978,393 individuals aged 76 to 79 years at the start of the vaccination period

172,145 individuals aged 80 to 83 years received their first dose between 15th and 20th December 2020

171,931 individuals aged 80-83 years who were not living in care homes received their first dose between 15th and 20th December 2020

1,912,024 individuals aged 76 to 79 were not living in care homes

170,226 individuals aged 80-83 years had no prior COVID and were eligible

1,889,891 individuals aged 76 to 79 had no prior COVID

38,302 individuals excluded:
- No record of COVID-19
- Gender
- Area of residence
- Small area deprivation;
- Ethnic group,
- Health status;
- Living arrangements;
- Seasonal influenza vaccine history since April 2020;
- Non-elective bed days in the two months prior to vaccination

1,887,634 individuals unvaccinated up to the last 2 weeks of the monitoring period and were eligible

Repeated for different reported monitoring period end dates

131,924 were matched to control

131,924 unvaccinated individuals aged 76-79 were included in the unvaccinated controls

688 excluded and were:
- A resident at the same address as the control
- In hospital at the time of the vaccination
- Matched to a control who was in hospital at the time of vaccination

131,236 (77.1% of 170,226 eligible cases) matched pairs

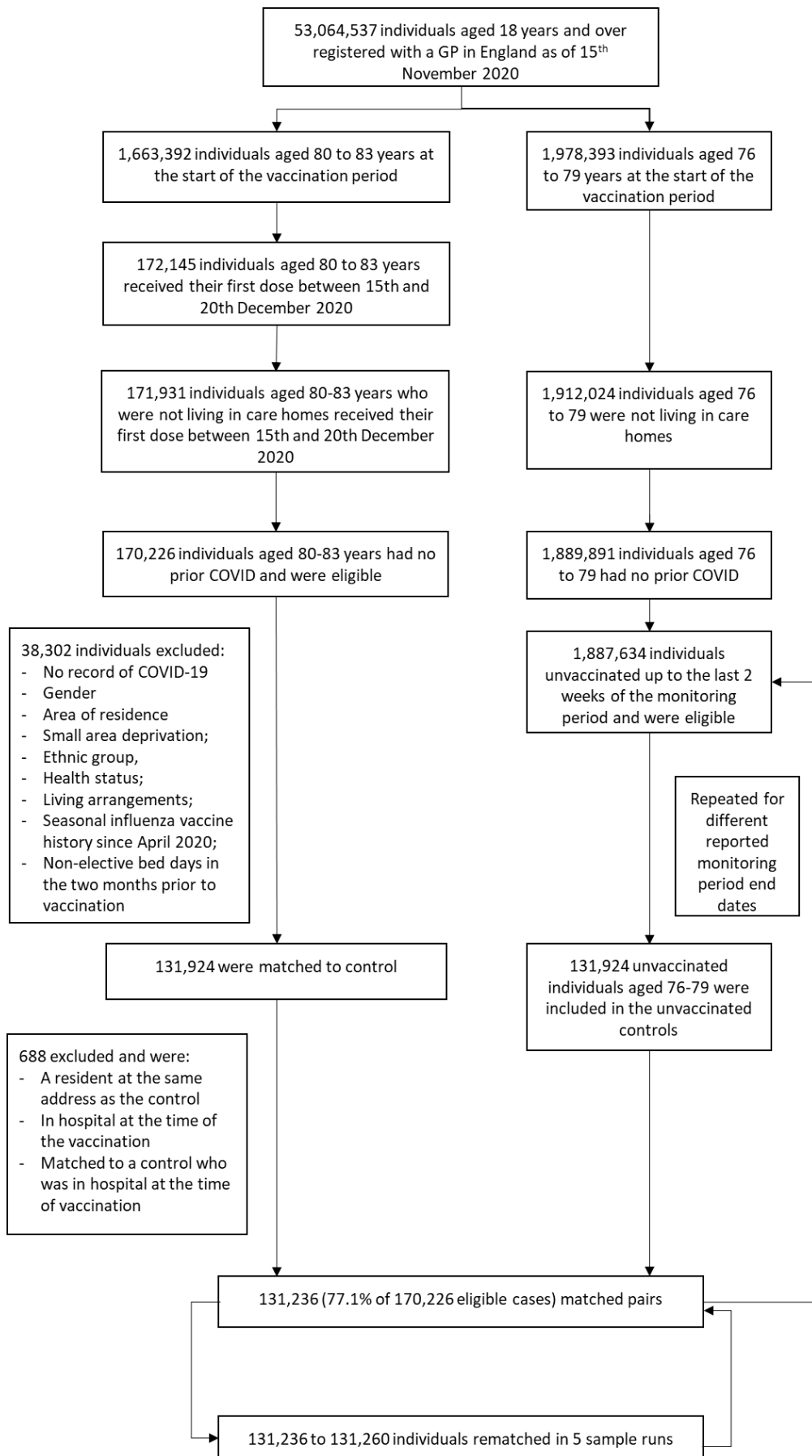131,236 to 131,260 individuals rematched in 5 sample runs

Table 1. Demographic and clinical characteristics of vaccinated persons and their unvaccinated controls based on the matched cohort at baseline (day 11 after vaccination).

Matching criteria	Categories	Total number of 80 to 83 year olds	Total number of 80 to 83 year olds vaccinated	Of which tested positive for COVID-19	Number with a pairwise control match	% with a pairwise match	% given a second dose by day 45
Gender	Female	869,792	89,930	153	69,819	77.6%	80.6%
	Male	793,599	80,295	162	61,417	76.5%	80.6%
	Unknown	<5	<5	-	-	0.0%	
Ethnicity	White	1,375,449	157,896	273	127,605	80.8%	80.5%
	Black	27,390	1,567	<5	270	17.2%	78.8%
	Pakistani and Bangladeshi	16,466	1,141	15	212	18.6%	86.4%
	Other BAME	55,180	5,922	23	1,803	30.4%	85.6%
	Unknown	188,907	3,700	<5	1,346	36.4%	80.3%
IMD Quintile	1 (most deprived)	272,565	23,292	42	17,135	73.6%	86.6%
	2	304,696	28,556	64	20,119	70.5%	81.7%
	3	347,849	35,785	71	26,927	75.2%	80.4%
	4	368,308	40,339	75	31,648	78.5%	79.5%
	5 (least deprived)	368,876	42,213	62	35,407	83.9%	78.3%
	Not recorded	1,098	41	<5	-	0.0%	
Living arrangements	Living with children	127,582	5,297	23	1,224	23.1%	81.7%
	Living alone	555,343	49,876	74	33,730	67.6%	81.5%
	All other living arrangements	980,467	115,053	218	96,282	83.7%	80.3%
Health Risk	Frail and/or clinically extremely vulnerable	317,750	42,856	128	28,903	67.4%	81.1%
	Clinically vulnerable	393,749	57,742	95	43,515	75.4%	80.1%
	Healthy/other	951,893	69,628	92	58,818	84.5%	80.7%
Flu vaccine	Received seasonal flu vaccine FY2020/21	948,840	150,300	263	118,746	79.0%	80.3%
	Did not receive seasonal flu vaccine FY2020/22	714,552	19,926	52	12,490	62.7%	83.1%
Recent acute illness	High	14,697	809	7	22	2.7%	52.4%
	Medium	8,701	521	<5	6	1.2%	100.0%
	Low	1,639,994	168,896	305	131,208	77.7%	80.6%
Region	East Midlands	149,390	8,830	13	7,211	81.7%	63.1%
	East of England	193,482	21,805	53	17,308	79.4%	78.5%
	London	173,844	18,923	87	10,901	57.6%	85.8%
	North East	89,680	9,300	8	7,314	78.6%	89.8%
	North West	231,339	22,898	31	18,312	80.0%	87.7%
	South East	279,419	29,011	64	22,674	78.2%	81.6%
	South West	192,927	21,349	19	17,319	81.1%	81.6%
	West Midlands	182,345	22,168	19	17,678	79.7%	68.9%
	Yorkshire and The Humber	169,606	15,882	20	12,519	78.8%	87.5%
	Unknown	1,360	60	<5	-	0.0%	
Total		**1,663,392**	**170,226**	**315**	**131,236**	**77.1%**	**80.6%**

Vaccine effectiveness

Across 45 days of follow-up, there were an average of 13.7 documented SARS-CoV-2 infections per day per 100,000 vaccinated individuals, compared to 23.2 per 100,000 unvaccinated controls. Over the same period, a daily average of 5.0 individuals per 100,000 attended A&E with Covid-19 and 5.3 per 100,000 were hospitalised with Covid-19 amongst the vaccinated cohort, compared to 9.6 per 100,000 (attended) and 9.4 per 100,000 (hospitalised) amongst unvaccinated controls.

For the unvaccinated comparison group, event rates increased in the first two weeks of follow-up, with documented infections reaching a maximum at day 20, and emergency hospital attendances and admissions peaking between days 23 and 26 (Figure 3). These profiles reflect the shape of the COVID-19 pandemic in England where prevalence peaked around the 1st January 2021,[18] and hospitalisations peaked in the second week of January 2021.[19] For the vaccinated group, documented infections peaked earlier (day 14) and hospitalisations peaked between days 23 and 26. We found similar results when we matched vaccinated individuals to unvaccinated individuals aged 72-75 years, and when the comparison group was restricted to individuals who remained unvaccinated throughout the follow-up period (Appendix 5).

Figure 3. Profiles of positive COVID-19 infections and emergency hospital attendances and admissions by days since first dose of vaccination. The data represent people aged between 80 to 83 years who received their first dose of the BNT162b2 mRNA Covid-19 vaccine between the 15th and 20th December 2020 with comparison to their matched controls. 95% confidence intervals are displayed as dashed lines.
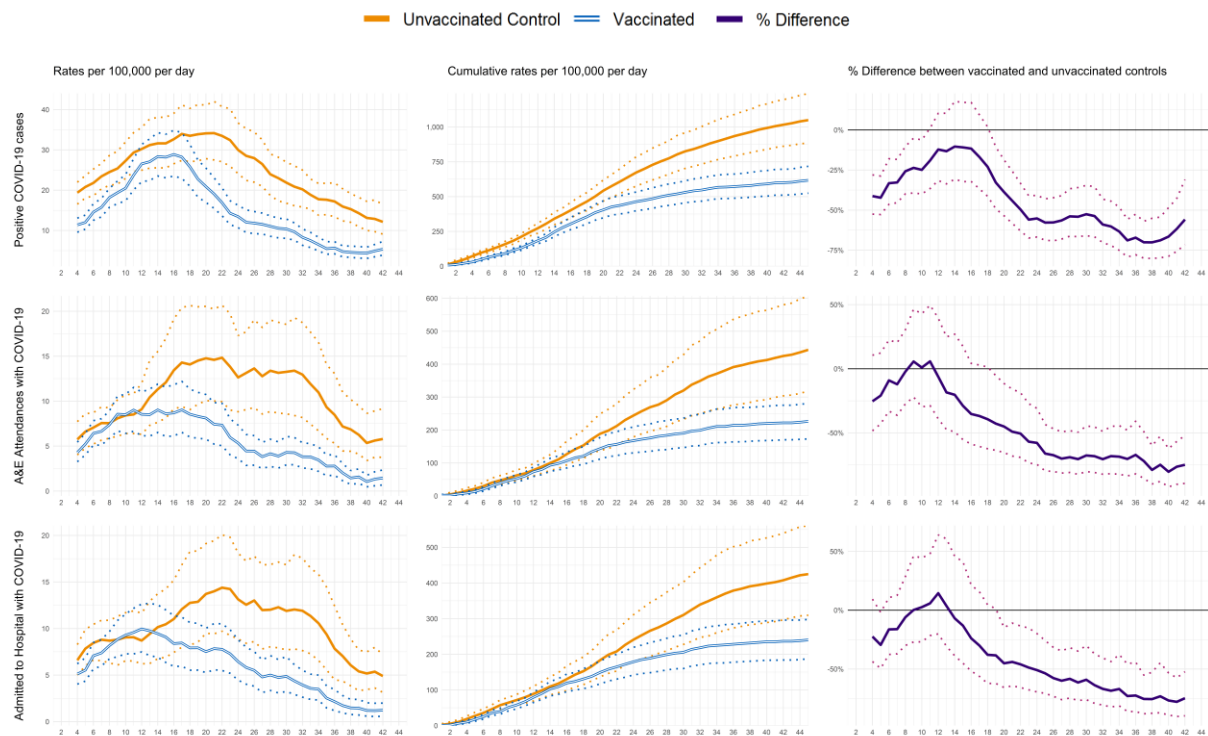

Table 2 shows vaccine effectiveness, defined as percentage difference between vaccinated and unvaccinated groups, for each outcome across four time-periods. Effectiveness increased over the follow-up period for all three outcomes. Estimated effectiveness at 21-27 days was 55.2% (95%CI 40.8%-66.8%) for documented infection, 57.8% (30.8%-74.5%) for emergency hospital attendances, and 50.1% (19.9%-69.5%) for admissions. By day 35-41, estimated effectiveness was 70.1% (55.1%-80.1%) for documented infection, 78.9% (60.0%-89.9%) for emergency hospital attendances, and 75.6% (52.8%-87.6%) for hospitalisations.

Table 2. Estimates of the effectiveness of the BNT162b2 mRNA Covid-19 vaccine by days since vaccination.

		Days since first vaccine dose							
Measure	**Cohort**	**14 to 20 days**		**21 to 27 days**		**28 to 34 days**		**35 to 41 days**	
Cohort	Size (% Match Rate)	130,719	(76.8%)	130,326	(76.5%)	129,099	(75.8%)	122,702	(72.1%)
Rate of positive COVID-19 tests per 100,000 people per day	Unvaccinated group	34.0	(27.4 to 41.2)	30.0	(24.1 to 36.7)	20.9	(16.2 to 26.1)	15.3	(12.0 to 19.2)
	Vaccinated group	28.2	(22.9 to 34.3)	13.4	(10.7 to 16.2)	9.7	(7.6 to 11.9)	4.6	(3.3 to 6.1)
	% Difference	-16.9%	(9.4% to -36.7%)	-55.2%	(-40.8% to -66.8%)	-53.7%	(-35.4% to -66.6%)	-70.1%	(-55.1% to -80.1%)
Rate of COVID-19 related A&E attendances per 100,000 people per day	Unvaccinated group	14.3	(9.4 to 20.4)	12.6	(8.8 to 17.3)	13.4	(8.4 to 19.3)	6.9	(4.4 to 10.2)
	Vaccinated group	9.0	(6.5 to 12.2)	5.3	(3.6 to 7.3)	4.3	(2.9 to 6.0)	1.5	(0.7 to 2.3)
	% Difference	-36.8%	(2.9% to -60.6%)	-57.8%	(-30.8% to -74.5%)	-68.1%	(-45.2% to -80.9%)	-78.9%	(-60.0% to -89.9%)
Rate of COVID-19 related hospital admissions per 100,000 people per day	Unvaccinated group	12.1	(8.0 to 16.8)	13.1	(8.8 to 18.1)	12.0	(7.8 to 17.9)	6.1	(3.8 to 8.9)
	Vaccinated group	8.4	(5.9 to 11.2)	6.4	(4.5 to 8.8)	4.4	(2.9 to 6.1)	1.5	(0.8 to 2.4)
	% Difference	-30.0%	(15.7% to -56.3%)	-50.1%	(-19.9% to -69.5%)	-63.7%	(-37.1% to -79.2%)	-75.6%	(-52.8% to -87.6%)

Discussion

Statement of principal findings

We compared rates of SARS-CoV-2 positive tests and Covid-19 hospitalisations in the 45-day period after 171,931 individuals aged 80 to 83 years in England received a first dose of BNT162b2 mRNA Covid-19 vaccine as part of the nationwide NHS vaccination campaign to rates for slightly younger individuals with the same characteristics who became eligible for vaccination later. Emergency admission was 50.1% (19.9% to 69.5%) less likely 21 to 27 days after vaccination and 75.6% (52.8% to 87.6%) less likely 35 to 41 days after first vaccination and 7 days after 80% had received their second dose. Covid-19 infection was 55.2% (40.8% to 66.8%) less likely 21 to 27 days after vaccination and 70.1% (55.1% to 80.1%) less likely 35 to 41 days after first vaccination and 7 days after 80% had received their second dose. Collectively these results are consistent with one dose of the BNT162b2 mRNA vaccine reducing events from 14 days after vaccination, with more effectiveness in reducing the severity of symptoms than preventing infection.

Strengths and weaknesses of the study

We focused on a large number of the oldest people at high risk of serious Covid-19 outcomes. We considered a period and country experiencing widespread transmission and large numbers of hospitalisations. This provided statistical precision in the effectiveness estimates within a short period. We exploited a precise age cut-off that determined access to the vaccine, which reduced bias from selection into treatment.

Nonetheless, there is a risk of bias from unmeasured confounding. We matched cases and controls on combinations of 12 personal, household and area variables. We also compared four measures of hospital use in the previous 18 months and history of negative SARS-CoV-2 tests (see Appendix 6). Cases did not have lower event rates and had higher use of hospital services and more community-based Covid-19 tests prior to vaccination. This likely reflects the age difference which may bias our estimates towards lower than true effectiveness.

The rich set of matching variables meant some cases were excluded because there was no control available. These exclusions were more likely for some populations, including minority ethnic groups and residents of London, but the included individuals had similar outcomes to the excluded individuals and the effectiveness results were similar when we matched on fewer variables (Appendix 4).

The speed of the rollout of the NHS vaccination programme in England into younger populations reduced the pool of similar people who had not been vaccinated. We adjusted for the selection bias this generated and assessed the robustness of this adjustment by comparing to a younger age group where the selection bias occurred later in the monitoring period.

Finally, we considered Covid-19 related hospitalisations as well as positive Covid-19 tests. Hospitalisations are less likely to be influenced by changes in attitudes after receiving a vaccine that may affect whether individuals seek Covid-19 tests, such as misperceptions of immunity or misinterpretations of symptoms as side effects.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Our results are broadly consistent with existing estimates of BNT162b vaccine effectiveness, despite variations in study design, participant demographics and outcome definitions. We estimate effectiveness against documented infection of approximately 55% after one dose, rising to 70% after the majority received a second dose. These estimates are relatively consistent with results from a

similar study in England (55% after one dose, 80% 7 days after all received a second dose),[8] for the older age group in a similar study in Israel (50% after one dose, 95% 7 days after all received a second dose),[5] and all-age results from an RCT (52% rising to 95%).[3] Our point estimate of effectiveness against hospitalisation with Covid-19 (76% 7 days after most received a second dose) is somewhat lower than, though statistically compatible with, other estimates (80-87%)[5,8].

Several factors likely contribute to these differences. First, our estimates are specifically for an older population where vaccine-induced immune responses may be sub-optimal[11]. In addition, our population included 20% of vaccinated individuals for whom the second dose was extended beyond the study period. This may explain the greater agreement with existing estimates for effectiveness 21-27 days after vaccination than for longer follow-up when second dose coverage varied between studies. Consistent with this, a study based in Scotland where the majority received only single dose BNT162b estimated 68% (53 to 79) effectiveness against hospitalisation at an equivalent timepoint (35-41 days post vaccination)[7], slightly lower than our estimate.

Finally, an important consideration in observational studies is bias in selection into the intervention group. While all existing studies used statistical methods to adjust for biases,[5,7,8] we exploited the precise age thresholds that determined temporal eligibility for vaccination, thereby reducing the risk of unmeasured confounding between cases and controls. Such biases are exacerbated with longer follow-up periods as those remaining unvaccinated become increasingly different from those vaccinated earlier. The divergence between our effectiveness estimates and those in other studies with longer follow-up may reflect less bias in our study design and adjustment methodology.

Meaning of the study: possible explanations and implications for clinicians and policymakers

We provide evidence of high real-world effectiveness of the original dosing schedule of the BNT162b2 mRNA Covid-19 vaccine in preventing infections and hospitalisations despite the widespread transmission of the B.1.1.7 variant shortly after the study population was vaccinated. There have been concerns about reduced vaccine effectiveness, though our data is consistent with mass vaccination data[5,7,8] and only slightly reduced neutralisation of B.1.1.7 pseudovirus relative to the Wuhan reference strain.[20]

Unanswered questions and future research

Our study provides rigorous evidence to support effectiveness of vaccination in the real-world amongst older people. Future research priorities include the optimal dosing regimen, the longevity of this protection and applicability to other variants, effectiveness amongst younger people and specific population subgroups, and effects on onward transmission and asymptomatic infection.

Ethics

Author contributions

Copyright/license for publication

Declaration of interests

Public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Data sharing statement

Data used in the study are not publicly available and may be obtained via NHS Digital (https://digital.nhs.uk/services/data-access-request-service-dars). The analysis scripts used for the evaluation are available at https://github.com/NHSEI-Analytics/nhs_covid19_effectiveness.

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Supplementary Appendices: Effects of BNT162b2 mRNA vaccine on Covid-19 infection and Hospitalisation among older people: matched case control study for England

Appendix 1: Data sources

NHS England & Improvement has access to person-level datasets for the entire population of England that provide information on who has been vaccinated, by date, vaccine type and dose, their age, gender and details of the address they live at, if they have had a prior COVID-19 infection (that is reported) and whether they go on to test positive for COVID-19 post vaccination. These datasets, that are collated by NHS Digital, Public Health England and the Office for National Statistics, include information on the contacts individuals had with the health service before and since being vaccinated, including A&E attendances and hospital admissions, and information regarding people who have since died. In combination, these datasets offer significant insights into what happens to people post their first vaccination dose to understand the effectiveness of the vaccines.

A Master Patient Index (MPI) data mart has been developed that includes details of all NHS registered patients in England. The MPI is built from extracts from the National Health Application and Infrastructure Services (NHAIS) system[1], and comprises a list of NHS registered patients including details of their gender, age, area of residence together with a variety of derived data items including whether they are a permanent resident of a care home (based on address matching to registered care home details from the Care Quality Commission), detail of house occupancy/living arrangements (of which three categories have been used for the pairwise matching methodology: living with children under 18 years, living alone, and all other living arrangements) and supplementary information sourced from the Indices of Multiple Deprivation (IMD) classification for 2019.[2]

Several data assets have been linked to the MPI based on NHS Number (using a common pseudonym within a secure environment in accordance with the Control of Patient Information (COPI) notice[3]) including:

- Vaccinations event data sourced from the National Immunisation Management Service (NIMS)[4] to provide details of the 1st and 2nd doses of the BNT162b2 mRNA and the ChAdOx1 adenovirus vector vaccines at person level. The extracts taken from the NIMS system undergo a series of transformations and data cleaning steps to identify events where vaccinations were given in line with those used for publication[5]. The dataset is also used to identify people who received a seasonal flu vaccine during FY2020/21;
- Hospital-based (Pillar 1) and community-based (Pillar 2) COVID-19 positive and negative tests data sourced from Public Health England Unified Sample Dataset[6]. For this analysis a dataset

prepared by PHE that provides details of the 1st positive polymerase-chain-reaction (PCR) COVID-19 test per individual is used;

- Death registrations sourced from the Office for National Statistics (ONS)[7];
- Accident and Emergency (A&E) attendance records sourced from the Emergency Care Dataset (ECDS) via NHS Digital[8];
- Admitted patient care hospitals spell records sourced from the Admitted Patient Care Commissioning Dataset (APC CDS)[9] via NHS Digital's SUS+ Service[10]; and
- Shielded Patient List as generated by NHS Digital using a series of patient level collections to identify clinically extremely vulnerable individuals.[11]

A number of derived data items have been incorporated into the data mart to provide information on the health status of individuals, including the 'Bridges to Health' segmentation model developed by Outcomes Based Healthcare[12] that identifies patients with co-morbidities that increase their risk of hospitalisation (here referred to as clinically vulnerable), and an algorithm applied to historic APC CDS spells data to identify frail individuals[13]. For the pairwise matching methodology, these data items have been combined into a measure of health status comprising three categories: frail and/or clinically extremely vulnerable, clinically vulnerable, and other/unknown (which predominately represents relatively healthy individuals).

Ethnicity data sourced from the 'Bridged to Health' model has been supplemented by data from NHS Digital sourced from a range of administrative sources include General Practice records. For the pairwise matching methodology four categories have been used: White, Black, Pakistani or Bangladeshi, other ethnicity, and ethnicity not reported. These categories are correlated with vaccine uptake in the wider population[14].

A weighted acute illness measure has been derived using completed APC CDS spells. Total non-elective occupied bed days for individuals discharged between 15th November and 14th December have been multiplied by two, and the equivalent measure for discharges between the 15th October 2020 and 14th November 2020 remain unadjusted, with the two values summed. Spells where an individual was admitted and discharged on the same day count as 0.5 bed days. The acute illness measure is then defined as follows: high non-elective bed use (6 plus weighted bed days); medium non-elective bed use (3 to 5 weighted bed days), and low/no non-elective bed use (0 to 2 weighted bed days).

The refresh cycle for the data sources used in this data mart are daily for the vaccinations, testing, mortality, A&E and APC datasets. The MPI is refreshed on a monthly cycle. The coverage, completeness and quality of these collections vary, and steps have been taken to ensure the data used in the evaluation are complete. The data mart used to generate the results presented in this analysis was extracted on the 9th February 2021 and includes complete records to the 3rd February 2021. This uses a cut of the MPI from mid-November 2020 and all age-based calculations reference individuals ages as of mid-November 2020.

Appendix 2: Matching and adjustment methodology

We matched vaccinated individuals in their early 80s to controls in their late 70s. This exploits the age-based eligibility criteria for the nationwide population vaccination[15], whereby people aged 80 years and over were prioritised for vaccination. Whilst this approach helps minimise these biases in the early stages of the vaccination programme, from mid-January 2021 significant numbers of 70-year-olds had received their 1st vaccine dose. Because we exclude individuals who were vaccinated more than 14 days

before the end of the monitoring period from the pool of potential controls, this generates bias whereby the proportion of people in the pool available for matching becomes enriched in people who test positive for COVID-19 as individuals should not have had a COVID-19 infection in the two weeks prior to vaccination. If unaccounted for, this selection bias artificially increases the number of COVID-19 positive people in the pairwise control relative to the vaccinated cohort (see Table A2-1).

Table A2-1. Summary of change in the number of people and COVID-19 status of people in the available for matching to vaccinated individuals as the monitoring period used in the evaluation is extended. The analysis has been run twice: once excluding controls that received their 1st COVID-19 dose during the monitoring period, and a second time excluding controls that received their 1st COVID-19 dose before 14 days of the end of the monitoring period (which is the approach used in the main analysis).

Days since vaccination	Total number of 80 to 83 year olds vaccinated	Pairwise matching excluding controls that received their 1st COVID-19 vaccine dose during the monitoring period					Pairwise matching excluding controls that received their 1st COVID-19 vaccine dose before 14 days of the end of the monitoring period				
		Total number of match pairs	% Match rate	Count of potential controls	Count of potential controls with a positive COVID-19 test result	Percentage of potential controls with a positive COVID-19 test result	Total number of match pairs	% Match rate	Count of potential controls	Count of potential controls with a positive COVID-19 test result	Percentage of potential controls with a positive COVID-19 test result
Day 11	170,424	129,939	76.2%	1,929,275	23,857	1.2%	131,236	77.0%	1,949,529	24,272	1.2%
Day 12	170,424	129,742	76.1%	1,926,965	23,823	1.2%	131,143	77.0%	1,948,512	24,262	1.2%
Day 13	170,424	129,519	76.0%	1,924,717	23,801	1.2%	131,031	76.9%	1,947,080	24,254	1.2%
Day 14	170,424	129,523	76.0%	1,924,321	23,796	1.2%	130,960	76.8%	1,945,651	24,242	1.2%
Day 15	170,424	129,474	76.0%	1,924,136	23,793	1.2%	130,816	76.8%	1,944,085	24,218	1.2%
Day 16	170,424	129,364	75.9%	1,922,923	23,777	1.2%	130,782	76.7%	1,942,649	24,207	1.2%
Day 17	170,424	129,116	75.8%	1,918,750	23,723	1.2%	130,736	76.7%	1,941,076	24,192	1.2%
Day 18	170,424	128,298	75.3%	1,899,266	23,531	1.2%	130,709	76.7%	1,940,620	24,173	1.2%
Day 19	170,424	127,295	74.7%	1,873,909	23,297	1.2%	130,695	76.7%	1,940,618	24,173	1.2%
Day 20	170,424	126,223	74.1%	1,854,501	23,118	1.2%	130,703	76.7%	1,940,612	24,173	1.2%
Day 21	170,424	125,200	73.5%	1,845,495	23,029	1.2%	130,671	76.7%	1,940,600	24,173	1.2%
Day 22	170,424	124,613	73.1%	1,838,815	22,924	1.2%	130,709	76.7%	1,940,548	24,173	1.2%
Day 23	170,424	123,842	72.7%	1,826,997	22,815	1.2%	130,667	76.7%	1,939,679	24,138	1.2%
Day 24	170,424	122,749	72.0%	1,796,769	22,549	1.3%	130,293	76.5%	1,934,746	23,971	1.2%
Day 25	170,424	120,994	71.0%	1,762,271	22,281	1.3%	129,880	76.2%	1,929,275	23,857	1.2%
Day 26	170,424	118,830	69.7%	1,720,682	21,961	1.3%	129,687	76.1%	1,926,965	23,823	1.2%
Day 27	170,424	116,564	68.4%	1,685,512	21,717	1.3%	129,516	76.0%	1,924,717	23,801	1.2%
Day 28	170,424	115,625	67.8%	1,670,879	21,604	1.3%	129,473	76.0%	1,924,321	23,796	1.2%
Day 29	170,424	114,915	67.4%	1,658,826	21,495	1.3%	129,487	76.0%	1,924,136	23,793	1.2%
Day 30	170,424	112,743	66.2%	1,603,655	21,166	1.3%	129,371	75.9%	1,922,923	23,777	1.2%
Day 31	170,424	109,937	64.5%	1,540,031	20,856	1.4%	129,098	75.8%	1,918,750	23,723	1.2%
Day 32	170,424	104,142	61.1%	1,456,681	20,405	1.4%	128,225	75.2%	1,899,266	23,531	1.2%
Day 33	170,424	96,619	56.7%	1,340,317	19,787	1.5%	127,282	74.7%	1,873,909	23,297	1.2%
Day 34	170,424	86,486	50.7%	1,213,893	19,224	1.6%	126,204	74.1%	1,854,501	23,118	1.2%
Day 35	170,424	83,476	49.0%	1,171,084	18,994	1.6%	125,156	73.4%	1,845,495	23,029	1.2%
Day 36	170,424	80,657	47.3%	1,132,764	18,774	1.7%	124,590	73.1%	1,838,815	22,924	1.2%
Day 37	170,424	77,236	45.3%	1,089,302	18,521	1.7%	123,798	72.6%	1,826,997	22,815	1.2%
Day 38	170,424	74,571	43.8%	1,049,609	18,255	1.7%	122,684	72.0%	1,796,769	22,549	1.3%
Day 39	170,424	69,833	41.0%	976,628	17,826	1.8%	120,955	71.0%	1,762,271	22,281	1.3%
Day 40	170,424	58,354	34.2%	858,984	17,189	2.0%	118,804	69.7%	1,720,682	21,961	1.3%
Day 41	170,424	46,962	27.6%	762,004	16,610	2.2%	116,539	68.4%	1,685,512	21,717	1.3%
Day 42	170,424	41,695	24.5%	714,711	16,285	2.3%	115,584	67.8%	1,670,879	21,604	1.3%
Day 43	170,424	37,394	21.9%	675,280	15,990	2.4%	114,908	67.4%	1,658,826	21,495	1.3%
Day 44	170,424	33,956	19.9%	645,526	15,663	2.4%	112,733	66.1%	1,603,655	21,166	1.3%
Day 45	170,424	31,200	18.3%	620,896	15,366	2.5%	109,906	64.5%	1,540,031	20,856	1.4%

To adjust for this bias, we have developed a methodology where we generate a number of daily timeseries for each outcome by extending the monitoring period a day at a time, starting with an end date 11 days post vaccination (at which point the bias is minimal) and repeating the process 35 times to extend the monitoring period to 45 days post vaccination. With each iteration the size of the potential pool of match pairs contracts as we exclude from the pool of potential controls individuals who were vaccinated more than 14 days before the end of the monitoring period.

We then align each timeseries so that vaccination events on the 15th, 16th, 17th, 18th, 19th and 20th December 2020 reference to day 0 with up to 45 days follow-up. The absolute numbers for each

outcome (positive tests, A&E attendances with COVID-19 and admissions with COVID-19 via A&E) to hospital) are converted into rate per 100,000 per day by dividing by the size of the matched cohort for each of the 35 runs.

Next we compare the total cumulative rate for each run to the previous day's run excluding the latest day from the former to calculate the change run-on-run (a_d) as below:

$$a_d = \left. \frac{\sum_{t=1}^{d-1} y_{t,d}^c}{} \middle/ \sum_{t=1}^{d-1} y_{t,d-1}^c \right.$$

where $y_{t,d}^c$ the event rate per 100,000 persons at time t for the control group, c represents the control cohort, t is the start date of the monitoring period (which is fix as Day 1), and d is the last day for each run. This generates a set of values for a_d that are applied to correct for the cumulative sampling bias using as follows:

$$\widetilde{y_{t,d}^c} = y_{t,d}^c \cdot \frac{1}{\prod_{d=1}^d a_d}$$

Following these steps, we generate a set of adjusted time series for each run for the controls and vaccinated cohorts as illustrated in Figure A2-1. For each run we take the latest value as the best estimate of the adjusted daily figure for that point in time as denoted by the dashed line.

Figure A2-1. Numbers of individuals testing positive for COVID-19 post vaccination (in blue) with a comparison to their match pairs (in orange) as a rate per 100,000. The left-hand charts present the raw numbers pre-adjustment for the sampling bias where each line represents to a different cut-off date for the analysis that varies the size of the pool of individuals available for matching. The right-hand charts present the adjusted figures based on the methodology, where the dashed blue and dashed orange lines represent the most complete estimate by day since vaccination.

(a) Matching methodology excluding people who received their 1st vaccine dose before the end of the monitoring period as a potential control
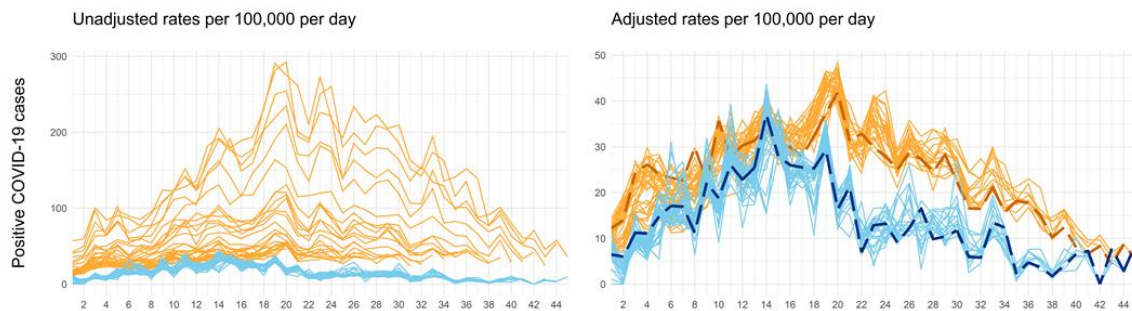
(b) Matching methodology excluding people who received their 1st vaccine dose before 14 days of the end of the monitoring period as a potential control
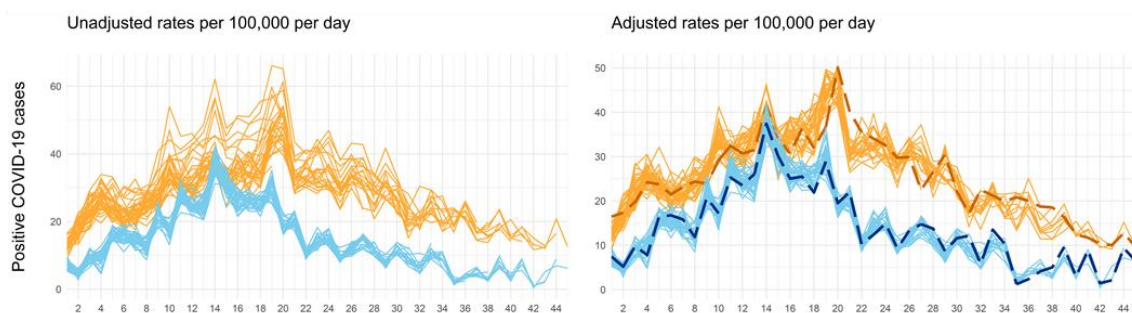
The process is repeated five times for five separate batches (where the matching process is repeated with different random number seeds, allowing replacement in match-pairs between the sensitivity runs). A simple average is taken across the five batches as follows:

$$y_{t,d}^c = \frac{1}{N} \sum_{n=1}^{N} y_{t,d,n}^c$$

We then run a bootstrapping procedure with replacement 100 times within each of the batches. This gives us 5x100 values for each of the key statistics (event rate in vaccinated, event rate in matched controls, relative reduction in event rate). We use the distribution of these statistics to generate 95% confidence intervals (by picking the 12th (0.025*500) lowest and highest values). For graphical purposes only, seven-day moving averages of the rates are calculated and presented.

Appendix 3: Measuring COVID-19 related emergency hospital attendances and admissions

Two outcome measures of hospitalisation with COVID-19 have been used in the evaluation: (1) A&E attendance with Covid-19 measured using the Emergency Care Data Set (ECDS), and (2) non-elective admission to hospital measured using the Admitted Patient Care Commissioning Dataset (APC CDS). Both datasets have timeliness issues with coverage and coding completeness that can bias analysis if not accounted for.

To circumvent issues with coding completeness, a matching algorithm has been used to identify COVID-19 related A&E attendances and admissions by combining diagnosis information available from the ECDS/APC records (see Table A3-1) with COVID-19 positive test results where the specimen was taken between 14 before and 6 days after the linked A&E attendance/admission. Using this matching window, 23% of linked test results were taken between 14 and 1 days before the A&E attendance, with 58% having a linked tests taken on days 0 to 1 post attendance, and 19% having a linked test taken between days 2 and 6 days post attendance (see Figure A3-1). Coding completeness is less of an issue with the APC CDS data, where the majority of COVID-19 related admissions both have a COVID-19 diagnosis on the APC record, and a linked COVID-19 positive test result (see Figure A3-2).

Table A3-1. List of SNOMED CT and ICD-10 codes used to identify 1st COVID-19 related A&E attendances and hospital admissions based on the primary diagnosis, secondary diagnoses, and (for ECDS) notifiable diseases fields within the ECDS and APC CDS collections. Several additional SNOMED CT codes are available for certain conditions that present with COVID-19, but an analysis suggest none of these codes (and other associated codes for COVID-19) have been used within the ECDS collection.

SNOMED CT Code/ ICD-10 Code	Description
1240751000000100	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 (disorder)
1240761000000102	Suspected coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 (situation)
1300721000000109	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 confirmed by laboratory test (situation)
U07.1	COVID-19, virus identified
U07.2	COVID-19, virus not identified
B97.2	Coronavirus as the cause of diseases classified to other chapters

Figure A3-1. Delay between specimen data for a COVID-19 positive test and the associated A&E attendance for 80- to 83-year-olds vaccinated between the 15th and 20th December 2020.
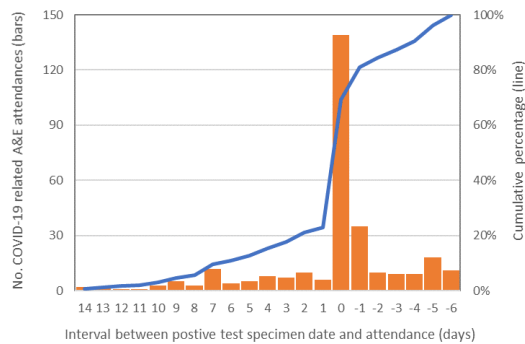
Figure A3-2. Counts of COVID-19 related A&E attendances and admissions for 80- to 83-year-olds vaccinated between the 15th and 20th December 2020 by method of identification, for (a) attendances, and (b) admissions.
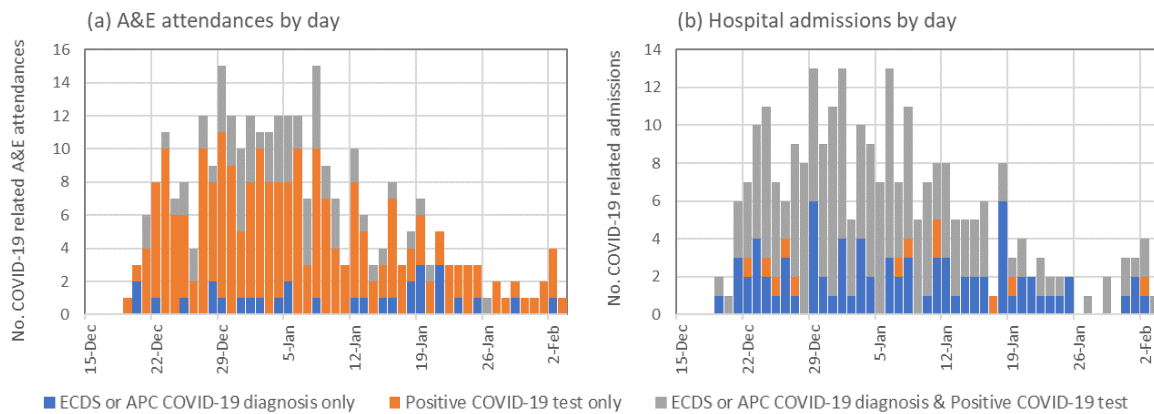
The matching algorithm allows all A&E attendances and/or admissions within this matching window to be counted as COVID-19 related, or it can be constrained to select the first COVID-19 related attendance and/or admission per person. Using the latter approach avoids counting multiple attendances and/or admissions for the same person and is the approach used in this analysis.

For the ACP CDS, an additional complication relates to the collection being discharge centric whereby providers usually only submit records for patients that has been discharged from hospital. To allow reporting by admission date, we restricted the analysis to patients who stayed in hospital 42 days or less. This excludes 5.7% of COVID-19 related spells for 80- to 83-year olds (based on patients discharged between the 8th December 2020 and the 31st March 2021).

To account for incomplete coverage of the ECDS collection, the analysis is based on A&E data for a sample of 118 NHS providers in England that have complete data to the 9th February 2021 based on an extract taken on the 9th March 2021. Similarly, to account for incomplete coverage of the APC CDS collection, the analysis is based on APC CDS data for a sample of 124 NHS providers in England that have complete data to the 17th March 2021 based on an extract taken on the 6th April 2021. These two samples accounts for 95% of Type 1&2 A&E attendances and 93% of admitted patient care spell for England. As the pairwise control matching methodology matches the vaccinated individual to a control from the same middle super output area, we do not expect a systematic bias in the analysis due to incomplete coverage.

These attendances and admissions are referred to as 'with' COVID-19 as the available data does not allow us to definitively determine if their COVID-19 infection was the primary reason for their A&E attendance or admission to hospital.

Appendix 4: Changing composition of the study population by follow-up period

The adjustment methodology described in Appendix 2 involves re-matching vaccinated individuals to controls as the follow-up period is extended a day at a time. Therefore, depending on the length of follow-up, the size and composition of both the vaccinated group and unvaccinated control group change. For example, in the main analysis, the match rate falls from 77.0% at day 11 (which represents the baseline case) to 64.5% at day 45 (Table A2-1).

Table A4-1 presents the number and percentage of vaccinated individuals for whom a pairwise match was identified at the mid-points of each period of follow-up, stratified by each matching variable. While there is wide variability in the percentage of vaccinated individuals with a matched pair (from 1.2% to 84.2%) across subgroups at day 17 of follow-up, the relative composition of those included in analysis is relatively stable across extended follow-up times (Table A4-1). The largest changes were for health status category where the share of the health/other category increases by 0.41 percentage points, with concurrent reductions of 0.22 and 0.18 percentage points for the frail and/or clinically extremely vulnerable and clinical vulnerable groups respectively between 17 and 38. These changes are small and are unlikely to result in any significant bias to the effectiveness estimates as the monitoring period is extended.

Table A4-1 also provides unadjusted and adjusted estimates of cumulative documented infections amongst vaccinated and unvaccinated control individuals by subgroup. These were generated by selecting all records without replacement and running the same adjustment process that was used in the bootstrapping process in the main analysis. Note that the main analysis bootstrapping process sampled with replacement, so values differ from those in the main analysis. We derived the ratio of adjusted to unadjusted total infections and applied this as a normalisation factor to each subgroup to estimate adjusted subgroup counts.

Table A4-1. Demographic and clinical characteristics of vaccinated persons and their unvaccinated controls based on matching to the 76 to 79 years population. Four matched cohort at days 17, 24, 31 and 38 post vaccination are presented, which relate to the mid-points of each period of follow-up. Cumulative unadjusted and adjusted rates of COVID-19 positive tests are included to demonstrate differences in test-positivity rates between the subgroups.

Matching criteria	Categories	Total Number of 80 to 83 year olds	Of which tested positive for COVID-19 by day 45 per 100,000	Days after vaccination 17							Days after vaccination 24							
				Number with a pairwise control match	% with a pairwise match	% of total match pairs	Vaccinated - tested positive for COVID per 100,000 (unadjusted)	Vaccinated - tested positive for COVID per 100,000 (adjusted)	Unvaccinated - tested positive for COVID per 100,000 (unadjusted)	Unvaccinated - tested positive for COVID per 100,000 (adjusted)	Number with a pairwise control match	% with a pairwise match	% of total match pairs	Vaccinated - tested positive for COVID (unadjusted)	Vaccinated - tested positive for COVID per 100,000 (unadjusted)	Vaccinated - tested positive for COVID per 100,000 (adjusted)	Unvaccinated - tested positive for COVID per 100,000 (unadjusted)	Unvaccinated - tested positive for COVID per 100,000 (adjusted)
Gender	Female	89,930	713	69,566	77.4%	53.2%	346.4	344.4	474.4	443.3	69,323	77.1%	53.2%	316	455.8	460.2	680.9	665.1
	Male	80,295	757	61,170	76.2%	46.8%	317.1	315.3	439.8	411.0	60,970	75.9%	46.8%	284	465.8	470.2	683.9	668.1
	Unknown	<5	-	-	0.0%	0.0%					-	0.0%	0.0%	-				
Ethnicity	White	157,896	690	127,137	80.5%	97.2%	325.6	323.7	449.9	420.5	126,706	80.2%	97.2%	568	448.3	452.6	668.5	653.0
	Black	1,567	1,595	270	17.2%	0.2%					270	17.2%	0.2%	3	1,111.1		1,111.1	
	Pakistani and Bangladeshi	1,141	3,243	210	18.4%	0.2%	2,381.0	2,367.1			210	18.4%	0.2%	6	2,857.1	2,884.4	2,857.1	2,790.9
	Other BAME	5,922	1,418	1,778	30.0%	1.4%	731.2	726.9	1,181.1	1,103.8	1,769	29.9%	1.4%	20	1,130.6	1,141.4	1,469.8	1,435.7
	Unknown	3,700	378	1,341	36.2%	1.0%					1,338	36.2%	1.0%	3	224.2		523.2	511.0
IMD Quintile	1 (most deprived)	23,292	992	17,045	73.2%	13.0%	416.5	414.1	580.8	542.8	16,993	73.0%	13.0%	98	576.7	582.2	847.4	827.8
	2	28,556	823	20,013	70.1%	15.3%	374.8	372.6	584.6	546.4	19,956	69.9%	15.3%	104	521.1	526.1	761.7	744.0
	3	35,785	819	26,801	74.9%	20.5%	328.3	326.4	421.6	394.0	26,744	74.7%	20.5%	128	478.6	483.2	676.8	661.1
	4	40,339	642	31,564	78.2%	24.1%	297.8	296.1	434.0	405.6	31,427	77.9%	24.1%	127	404.1	408.0	661.9	646.5
	5 (least deprived)	42,213	545	35,313	83.7%	27.0%	303.0	301.2	376.6	352.0	35,173	83.3%	27.0%	143	406.6	410.4	580.0	566.5
	Not recorded	41	2,439	-	0.0%	0.0%					-	0.0%	0.0%	-				
Living arrangements	Living with children	5,297	1,793	1,209	22.8%	0.9%	661.7	657.8	744.4	695.7	1,204	22.7%	0.9%	12	996.7	1,006.2	1,578.1	1,541.5
	Living alone	49,876	664	33,613	67.4%	25.7%	318.3	316.5	482.0	450.4	33,471	67.1%	25.7%	153	457.1	461.5	648.3	633.3
	All other living arrangements	115,053	715	95,914	83.4%	73.4%	333.6	331.7	446.2	417.0	95,618	83.1%	73.4%	435	454.9	459.3	682.9	667.1
Health Risk	Frail and/or clinically extremely vulnerable	42,856	1,199	28,780	67.2%	22.0%	517.4	514.7	667.1	623.5	28,614	66.8%	22.0%	216	754.9	762.1	1,044.9	1,020.7
	Clinically vulnerable	57,742	727	43,300	75.0%	33.1%	330.3	328.3	480.4	448.9	43,147	74.7%	33.1%	201	465.8	470.3	748.6	731.2
	Healthy/other	69,628	452	58,656	84.2%	44.9%	243.8	242.4	339.3	317.1	58,532	84.1%	44.9%	183	312.6	315.6	456.2	445.6
Flu vaccine	Received seasonal flu vaccine FY2020/21	150,300	710	118,292	78.7%	90.5%	323.8	321.9	467.5	436.9	117,906	78.4%	90.5%	530	449.5	453.8	681.9	666.1
	Did not received seasonal flu vaccine FY2020/22	19,926	913	12,444	62.5%	9.5%	417.9	415.4	369.7	345.5	12,387	62.2%	9.5%	70	565.1	570.5	686.2	670.3
Recent acute illness	High	809	3,214	22	2.7%	0.0%	-		-		22	2.7%	0.0%	-	-		4,545.5	
	Medium	521	3,647	6	1.2%	0.0%	-				6	1.2%	0.0%	-	-		-	
	Low	168,896	713	130,708	77.4%	100.0%	332.8	330.9	458.3	428.3	130,265	77.1%	100.0%	600	460.6	465.0	681.7	665.9
Region	East Midlands	8,830	657	7,131	80.8%	5.5%	252.4	250.9	350.6	327.6	7,115	80.6%	5.5%	29	407.6	411.5	646.5	631.5
	East of England	21,805	807	17,276	79.2%	13.2%	445.7	443.1	497.8	465.2	17,262	79.2%	13.2%	101	585.1	590.7	724.1	707.3
	London	18,923	1,575	10,804	57.1%	8.3%	814.5	809.8	1,055.2	986.1	10,708	56.6%	8.2%	102	952.6	961.7	1,512.9	1,477.8
	North East	9,300	419	7,323	78.7%	5.6%	163.9	162.9	587.2	548.8	7,257	78.0%	5.6%	23	316.9	320.0	744.1	726.9
	North West	22,898	751	18,200	79.5%	13.9%	340.7	338.7	450.5	421.1	18,145	79.2%	13.9%	93	512.5	517.4	760.5	742.9
	South East	29,011	707	22,580	77.8%	17.3%	367.6	365.4	451.7	422.2	22,516	77.6%	17.3%	115	510.7	515.6	759.5	741.9
	South West	21,349	436	17,290	81.0%	13.2%	156.2	155.2	214.0	200.0	17,190	80.5%	13.2%	45	261.8	264.3	337.4	329.6
	West Midlands	22,168	623	17,623	79.5%	13.5%	221.3	220.0	408.6	381.8	17,596	79.4%	13.5%	57	323.9	327.0	500.1	488.5
	Yorkshire and The Humber	15,882	434	12,509	78.8%	9.6%	231.8	230.5	303.8	283.9	12,504	78.7%	9.6%	35	279.9	282.6	375.9	367.2
	Unknown	60		-	0.0%	0.0%					-	0.0%	0.0%	-				
Total		**170,226**	**733**	**130,736**	**76.8%**	**100.0%**	**332.7**	**330.8**	**458.2**	**428.2**	**130,293**	**76.5%**	**100.0%**	**600**	**460.5**	**464.9**	**682.3**	**666.5**

Table A4-1 (Cont.) Demographic and clinical characteristics of vaccinated persons and their unvaccinated controls based on matching to the 76 to 79 years population. Four matched cohort at days 17, 24, 31 and 38 post vaccination are presented, which relate to the mid-points of each period of follow-up. Cumulative unadjusted and adjusted rates of COVID-19 positive tests are included to demonstrate differences in test-positivity rates between the subgroups.

Matching criteria	Categories	Total Number of 80 to 83 year olds	Of which tested positive for COVID-19 by day 45 per 100,000	Days after vaccination 31 — Number with a pairwise control match	% with a pairwise match	% of total match pairs	Vaccinated - tested positive for COVID per 100,000 (unadjusted)	Vaccinated - tested positive for COVID per 100,000 (adjusted)	Unvaccinated - tested positive for COVID per 100,000 (unadjusted)	Unvaccinated - tested positive for COVID per 100,000 (adjusted)	Days after vaccination 38 — Number with a pairwise control match	% with a pairwise match	% of total match pairs	Vaccinated - tested positive for COVID (unadjusted)	Vaccinated - tested positive for COVID per 100,000 (unadjusted)	Vaccinated - tested positive for COVID per 100,000 (adjusted)	Unvaccinated - tested positive for COVID per 100,000 (unadjusted)	Unvaccinated - tested positive for COVID per 100,000 (adjusted)
Gender	Female	89,930	713	68,684	76.4%	53.2%	531.4	530.3	861.9	824.6	65,285	72.6%	53.2%	370	566.7	565.6	1,066.1	953.4
	Male	80,295	757	60,414	75.2%	46.8%	559.5	558.3	902.1	863.1	57,399	71.5%	46.8%	347	604.5	603.3	1,097.6	981.6
	Unknown	<5	-	-	0.0%	0.0%					-	0.0%	0.0%	-				
Ethnicity	White	157,896	690	125,543	79.5%	97.2%	531.3	530.2	869.0	831.4	119,357	75.6%	97.3%	681	570.6	569.4	1,065.7	953.1
	Black	1,567	1,595	270	17.2%	0.2%	2,222.2	2,217.7	1,111.1		253	16.1%	0.2%	6	2,371.5	2,366.6	1,185.8	
	Pakistani and Bangladeshi	1,141	3,243	210	18.4%	0.2%	2,857.1	2,851.3	2,857.1	2,733.6	188	16.5%	0.2%	7	3,723.4	3,715.7	3,191.5	2,854.2
	Other BAME	5,922	1,418	1,749	29.5%	1.4%	1,200.7	1,198.2	1,715.3	1,641.1	1,632	27.6%	1.3%	20	1,225.5	1,222.9	2,328.4	2,082.3
	Unknown	3,700	378	1,326	35.8%	1.0%	226.2		527.9	505.1	1,254	33.9%	1.0%	3	239.2		558.2	499.2
IMD Quintile	1 (most deprived)	23,292	992	16,858	72.4%	13.1%	711.8	710.4	996.6	953.5	16,001	68.7%	13.0%	134	837.4	835.7	1,456.2	1,302.2
	2	28,556	823	19,817	69.4%	15.4%	595.4	594.2	1,059.7	1,013.9	18,720	65.6%	15.3%	114	609.0	607.7	1,314.1	1,175.2
	3	35,785	819	26,460	73.9%	20.5%	559.3	558.2	959.9	918.4	25,182	70.4%	20.5%	158	627.4	626.1	1,064.3	951.8
	4	40,339	642	31,129	77.2%	24.1%	472.2	471.3	812.7	777.6	29,608	73.4%	24.1%	149	503.2	502.2	945.7	845.7
	5 (least deprived)	42,213	545	34,834	82.5%	27.0%	488.0	487.0	723.4	692.1	33,173	78.6%	27.0%	162	488.3	487.3	901.3	806.1
	Not recorded	41	2,439	-	0.0%	0.0%					-	0.0%	0.0%	-				
Living arrangements	Living with children	5,297	1,793	1,188	22.4%	0.9%	1,262.6	1,260.0	1,431.0	1,369.1	1,100	20.8%	0.9%	13	1,181.8	1,179.4	1,636.4	1,463.4
	Living alone	49,876	664	33,115	66.4%	25.7%	504.3	503.3	839.5	803.2	31,250	62.7%	25.5%	177	566.4	565.2	982.4	878.6
	All other living arrangements	115,053	715	94,795	82.4%	73.4%	549.6	548.5	888.2	849.8	90,334	78.5%	73.6%	527	583.4	582.2	1,108.1	991.0
Health Risk	Frail and/or clinically extremely vulnerable	42,856	1,199	28,283	66.0%	21.9%	901.6	899.8	1,371.8	1,312.5	26,644	62.2%	21.7%	257	964.6	962.6	1,681.4	1,503.7
	Clinically vulnerable	57,742	727	42,680	73.9%	33.1%	545.9	544.8	1,014.5	970.6	40,380	69.9%	32.9%	240	594.4	593.1	1,238.2	1,107.4
	Healthy/other	69,628	452	58,135	83.5%	45.0%	369.8	369.1	543.6	520.0	55,660	79.9%	45.4%	220	395.3	394.4	679.1	607.3
Flu vaccine	Received seasonal flu vaccine FY2020/21	150,300	710	116,792	77.7%	90.5%	525.7	524.6	881.1	842.9	110,830	73.7%	90.3%	630	568.4	567.3	1,094.5	978.8
	Did not received seasonal flu vaccine FY2020/22	19,926	913	12,306	61.8%	9.5%	723.2	721.7	877.6	839.7	11,854	59.5%	9.7%	87	733.9	732.4	953.3	852.5
Recent acute illness	High	809	3,214	22	2.7%	0.0%	-		4,545.5		21	2.6%	0.0%	-	-		9,523.8	
	Medium	521	3,647	5	1.0%	0.0%	-		-		<5	0.8%						
	Low	168,896	713	129,071	76.4%	100.0%	544.7	543.5	880.1	842.1	122,659	72.6%	100.0%	717	584.5	583.3	1,079.4	965.3
Region	East Midlands	8,830	657	7,085	80.2%	5.5%	550.5	549.3	733.9	702.2	6,771	76.7%	5.5%	38	561.2	560.0	974.7	871.7
	East of England	21,805	807	17,138	78.6%	13.3%	630.2	628.9	910.3	870.9	16,683	76.5%	13.6%	113	677.3	675.9	1,138.9	1,018.5
	London	18,923	1,575	10,539	55.7%	8.2%	1,176.6	1,174.2	1,878.7	1,797.5	9,782	51.7%	8.0%	120	1,226.7	1,224.2	2,259.3	2,020.5
	North East	9,300	419	7,183	77.2%	5.6%	348.0	347.3	863.1	825.8	6,811	73.2%	5.6%	24	352.4	351.6	1,057.1	945.4
	North West	22,898	751	17,913	78.2%	13.9%	619.7	618.4	949.0	908.0	16,742	73.1%	13.6%	118	704.8	703.3	1,164.7	1,041.6
	South East	29,011	707	22,424	77.3%	17.4%	588.7	587.5	869.6	832.0	21,232	73.2%	17.3%	129	607.6	606.3	1,135.1	1,015.1
	South West	21,349	436	16,940	79.3%	13.1%	318.8	318.1	543.1	519.6	16,247	76.1%	13.2%	58	357.0	356.2	547.8	489.9
	West Midlands	22,168	623	17,381	78.4%	13.5%	402.7	401.9	817.0	781.6	16,388	73.9%	13.4%	79	482.1	481.1	1,037.3	927.7
	Yorkshire and The Humber	15,882	434	12,495	78.7%	9.7%	320.1	319.5	560.2	536.0	12,028	75.7%	9.8%	38	315.9	315.3	681.7	609.7
	Unknown	60		-	0.0%	0.0%					-	0.0%	0.0%	-				
Total		**170,226**	**733**	**129,098**	**75.8%**	**100.0%**	**544.5**	**543.4**	**880.7**	**842.6**	**122,684**	**72.1%**	**100.0%**	**717**	**584.4**	**583.2**	**1080.8**	**966.6**

Appendix 5: Comparison of vaccinated and unvaccinated controls pre-vaccination programme

The pairwise matching approach has been developed to include information on the socio-demographic characteristics of individuals who have been vaccinated, together with factors that are likely to be associated with individuals' exposure risk to COVID-19 including the local prevalence of COVID-19 (as captured by the MSOA of residence) and individuals living arrangements (with those living alone being more likely to have interactions with formal and informal carers). The matching approach also accounts for individuals' susceptibility to developing COVID-19 and the severity of illness experienced, and factors associated with individuals' behaviours that might predict their chances of being vaccinated.

A logistic regression model was used to test the statistical-significance of the parameters used in the pairwise matching approach for test positivity for COVID-19. Odd ratios for the regression are presented in Table A5-1. These results demonstrate that the majority of parameters used are significantly associated with individuals risk of developing COVID-19 during the monitoring period for the study.

Table A5-1. Adjusted odds ratios generated using a logistic regression model to predict test positivity between days 14 and 41 post vaccination event for vaccinated individuals and their pairwise controls. The model is based on data to day 41 post vaccination for 116,539 match pairs.

Reference Group	Parameter	Adjusted Odds Ratio	Upper CI 95%	Lower CI 95%	P value	Sign.
	Intercept	0.03	0.01	0.13	0.00	***
Unvaccinated	Vaccinated	0.43	0.40	0.47	0.00	***
Female: 80-82 matched to 78-79	Female: 82-83 matched to 78-79	1.00	0.89	1.12	0.97	
	Male: 80-81 matched to 76-77	1.01	0.90	1.13	0.88	
	Male: 82-83 matched to 78-79	0.99	0.88	1.11	0.81	
Ethnic Group: White	Ethnic Group: Black	1.58	0.81	3.07	0.18	
	Ethnic Group: Other BAME	1.98	1.54	2.56	0.00	***
	Ethnic Group: Pakistani and Bangladeshi	2.95	1.70	5.11	0.00	***
	Ethnic Group: Unknown	0.66	0.36	1.20	0.17	
Health Risk: Low/Unknown	Health Risk: Frail and/or clinically extremely vulnerable	2.37	2.14	2.62	0.00	***
	Health Risk: Clinically vulnerable	1.61	1.46	1.78	0.00	***
Living Arrangements: Other	Living Arrangements: Living with children	1.30	0.91	1.86	0.15	
	Living Arrangements: Living alone	0.88	0.79	0.97	0.01	**
IMD Quintile 3	IMD Quintile 1	1.29	1.13	1.47	0.00	***
	IMD Quintile 2	1.06	0.93	1.21	0.37	
	IMD Quintile 4	0.87	0.77	0.98	0.03	*
	IMD Quintile 5	0.85	0.75	0.95	0.01	**
Did not receive seasonal flu vaccine	Received seasonal flu vaccine	0.95	0.83	1.09	0.48	
No/low non-elective bed use	Medium & High non-elective bed use	0.34	0.08	1.41	0.14	

There may be other factors that are not accounted for by this matching approach that impact the outcomes being monitored. One approach for assessing if such unobserved biases are significant is to monitor outcomes for the intervention and control groups in the period before the intervention to assess how the intervention and control groups comparable. As the outcomes of interest for this evaluation are related to the first case of COVID-19 per person, we cannot do this directly. However, by comparing emergency hospital attendances, emergency hospital stays, outpatient attendances, and planned hospital stays over the period prior to the introduction of the vaccination programme for the vaccinated and control cohorts, we can assess how the matching approach performs in terms of healthcare utilisation (see Figure A5-1).

Figure A5-1. Comparison of the use of hospital-based services per day for the vaccinated group of 80 to 83 years olds (in blue) and the unvaccinated pairwise control group of 76 to 79 years olds (in orange) by activity type. Each data point reflects the daily total, and the solid lines present the seven-day centred moving averages. Data are sourced from the Emergency care Dataset, and the Outpatient and Admitted patient care datasets sourced from the SUS+ service and represent the baseline cohort of 131,236 match pairs at Day 11 post vaccination.
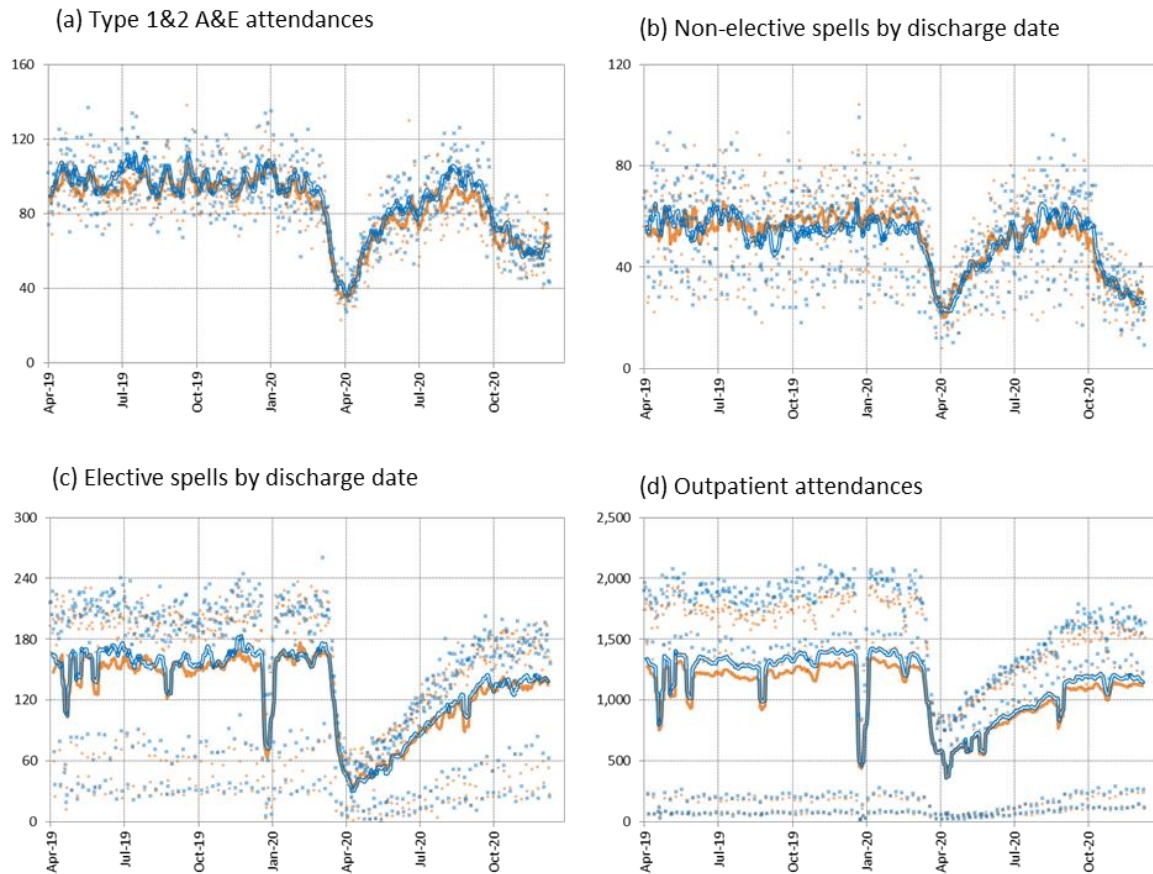
These results demonstrate a close match between the vaccinated and control cohorts in the 18 months to October 2020 for all four activity types. For planned care the vaccinated group is more likely to have used hospital-based health services in the previous 18 months, which is consistent with the vaccinated cohort being an average of 4 years older than their pairwise controls.

The number of negative tests undertaken for individuals within the vaccinated cohort and the control cohort are presented in Figure A5-2. As with the hospital activity measures, the number of negative tests undertaken is similar between the two groups, with the Pillar 1 negative tests (which represents those undertaken following contacts with the health system) showing a closer match when compared to Pillar 2 tests (which represent tests undertaken in the community) where the control group shows higher numbers of negative tests compared to the vaccinated group. This difference in Pillar 2 testing data is consistent with higher uptake rates of Pillar 2 tests by younger age groups, reflecting the average age difference of 4 years between the vaccinated and control groups.

Figure A5-2. Comparison of the number of negative COVID-19 tests by specimen date undertaken between the 1st May and 30th November 2020 for the vaccinated group and unvaccinated control. Each data point reflects the daily total, and the solid lines present the seven-day centred moving averages.
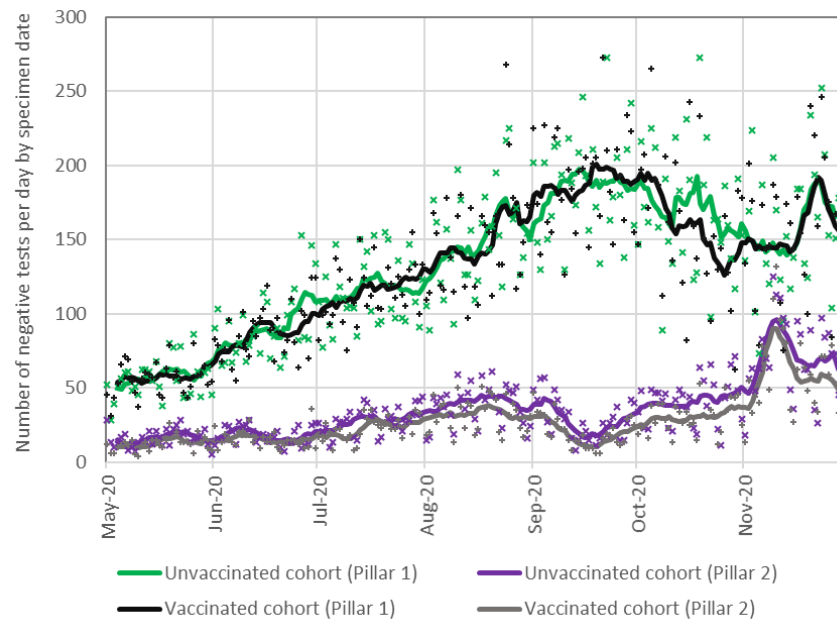
Overall, Figures A5-1 and A5-2 demonstrate a close match between the vaccinated and control groups before vaccination. These results, couple with the broad range of factors that are accounted for with the pairwise control matching process provides confidence the vaccinated control and matched controls are comparable and can be used to monitor outcomes.

Appendix 6: Sensitivity of outcomes to control selection

Due to the rapid vaccination rollout, controls who were ineligible for vaccination at the start of the follow-up period relatively quickly become eligible for vaccination (Figure 1 in the main text). This depleted the pool of available controls for matching at later stages of follow-up. In addition, those with documented infection during the study period became concentrated in the control group because, in order to take up vaccination, individuals must not have had documented infection in the preceding two weeks. To adjust for this selection bias, we used a novel adjustment methodology (Methods & Appendix 2).

To test the sensitivity of our results to possible residual selection bias, we repeated analysis matching 80-83-year-old vaccinated individuals to 72-75-year-old unvaccinated controls, as this group became eligible for vaccination later than the control group used in the main analysis (Figure 1). We also tested the sensitivity of the results to using only controls who remained unvaccinated throughout the follow-up period. Finally, for hospital admissions we included an additional outcome measure for patients admitted via A&E based on a disposal code of admitted to hospital, transferred to another provider or died as recorded in the Emergency Care Data Set.

Effectiveness estimates were broadly consistent whichever control population was used (see Figure A6-1 and Table A6-1). Effectiveness estimates were also consistent between the two measures of hospital admission.

Figure A6-1. Percentage difference in positive COVID-19 tests, A&E attendances with COVID-19, hospital admission via A&E with COVID-19 and all <43-day length of stay hospital admissions with COVID-19 for four matching strategies by day since first vaccine dose. 95% confidence intervals are represented by the dashed lines.
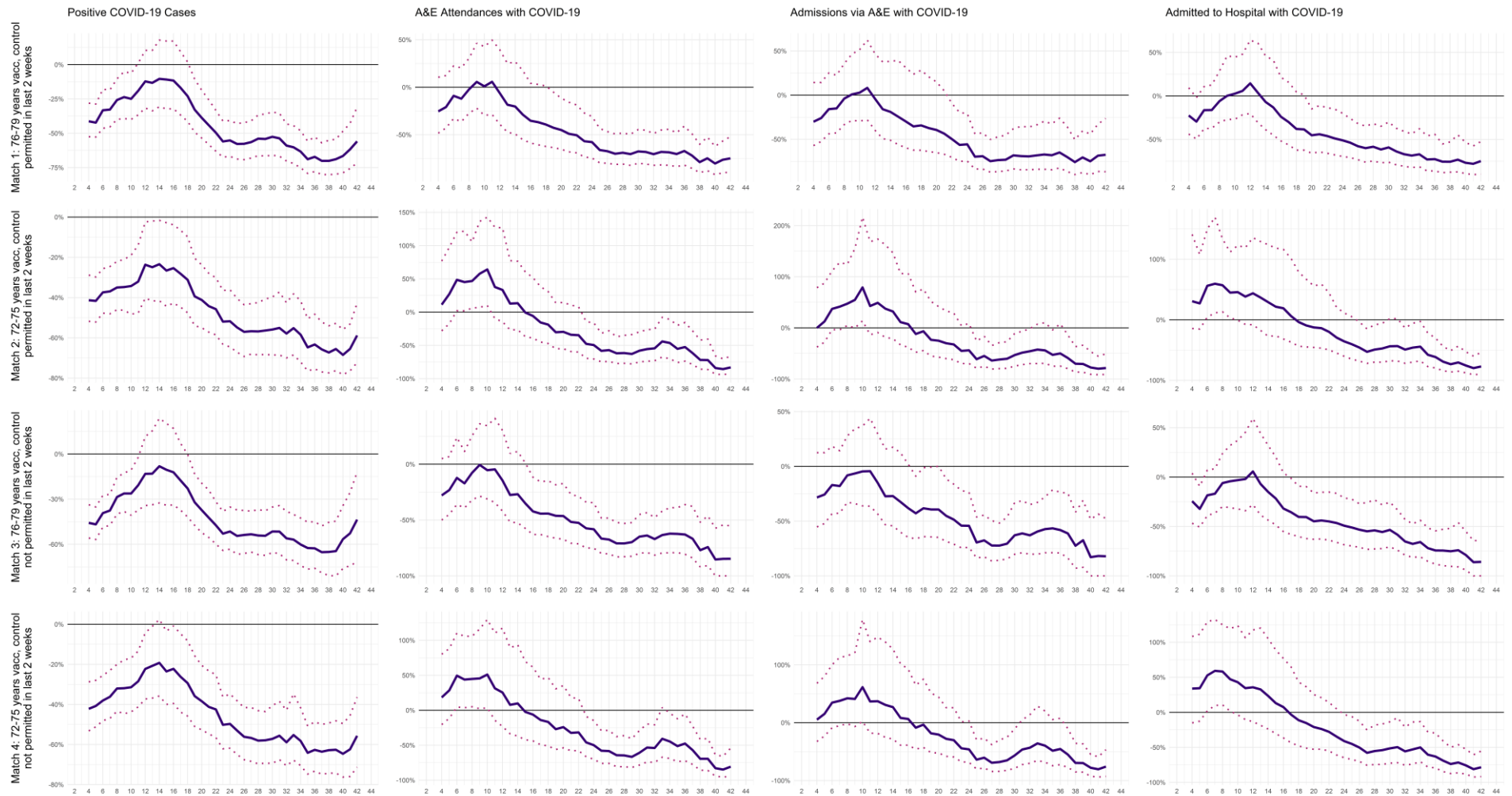
Table A6-1. Comparison of estimates of the effectiveness of the BNT162b2 mRNA Covid-19 vaccine by days since vaccination for four matching strategies.

		Days since first vaccine dose							
Control/Outcome	**Measure**	**14 to 20**		**21 to 27**		**28 to 34**		**35 to 41**	
Controls aged 76 - 79 years excluding those vaccinated before 14 days of the end of the monitoring period									
Cohort	Size (% Match Rate)	76.8%		76.5%		75.8%		72.1%	
Rate of positive COVID-19 tests	Vaccinated group	28.2	(34.3 to 22.9)	13.4	(16.2 to 10.7)	9.7	(11.9 to 7.6)	4.6	(6.1 to 3.3)
	Unvaccinated group	34.0	(41.2 to 27.4)	30.0	(36.7 to 24.1)	20.9	(26.1 to 16.2)	15.3	(19.2 to 12.0)
	% Difference	-16.9%	(9.4% to -36.7%)	-55.2%	(-40.8% to -66.8%)	-53.7%	(-35.4% to -66.6%)	-70.1%	(-55.1% to -80.1%)
Rate of COVID-19 realated A&E attendances	Vaccinated group	9.0	(12.2 to 6.5)	5.3	(7.3 to 3.6)	4.3	(6.0 to 2.9)	1.5	(2.3 to 0.7)
	Unvaccinated group	14.3	(20.4 to 9.4)	12.6	(17.3 to 8.8)	13.4	(19.3 to 8.4)	6.9	(10.2 to 4.4)
	% Difference	-36.8%	(2.9% to -60.6%)	-57.8%	(-30.8% to -74.5%)	-68.1%	(-45.2% to -80.9%)	-78.9%	(-60.0% to -89.9%)
Rate of COVID-19 related hospital admissions via A&E	Vaccinated group	6.7	(9.6 to 4.6)	4.4	(6.4 to 2.9)	3.4	(5.0 to 2.1)	1.3	(2.2 to 0.6)
	Unvaccinated group	10.3	(15.8 to 6.0)	9.9	(14.5 to 5.9)	10.9	(16.6 to 5.6)	5.3	(8.1 to 3.2)
	% Difference	-35.4%	(23.6% to -62.3%)	-55.7%	(-20.8% to -74.6%)	-69.0%	(-35.3% to -84.5%)	-75.8%	(-50.5% to -89.9%)
Rate of COVID-19 hospital admissions	Vaccinated group	8.5	(11.2 to 5.9)	6.4	(8.8 to 4.5)	4.4	(6.12 to 2.9)	1.5	(2.4 to 0.8)
	Unvaccinated group	12.1	(16.8 to 8.0)	13.1	(18.1 to 8.9)	12.0	(17.9 to 7.8)	6.1	(8.9 to 3.8)
	% Difference	-30.0%	(15.7% to -56.3%)	-51.0%	(-19.9% to -69.5%)	-63.7%	(-37.1% to -79.2%)	-75.6%	(-52.8% to -87.6%)
Controls aged 76 - 79 years excluding those vaccinated before the end of the monitoring period									
Cohort	Size (% Match Rate)	75.8%		72.1%		64.6%		43.8%	
Rate of positive COVID-19 tests	Vaccinated group	28.6	(34.3 to 23.4)	14.1	(17.3 to 11.1)	10.3	(13.2 to 7.7)	4.4	(6.6 to 2.5)
	Unvaccinated group	34.7	(41.2 to 28.9)	29.1	(34.9 to 23.8)	21.3	(25.1 to 17.9)	12.7	(15.3 to 10.3)
	% Difference	-17.6%	(7.1% to -37.2%)	-51.5%	(-35.2% to -63.3%)	-51.6%	(-34.3% to -66.2%)	-65.1%	(-45.4% to -80.8%)
Rate of COVID-19 realated A&E attendances	Vaccinated group	8.7	(11.7 to 6.2)	5.1	(7.1 to 3.3)	4.5	(6.4 to 2.9)	1.3	(2.5 to 0.5)
	Unvaccinated group	15.6	(20.3 to 11.6)	12.3	(16.0 to 8.9)	12.5	(16.0 to 9.3)	5.8	(7.8 to 4.2)
	% Difference	-44.3%	(-15.8% to -63.6%)	-58.2%	(-34.5% to -75.2%)	-63.9%	(-43.3% to -79.0%)	-77.0%	(-51.9% to -92.1%)
Rate of COVID-19 related hospital admissions via A&E	Vaccinated group	6.3	(9.1 to 4.1)	4.1	(6.2 to 2.5)	3.6	(5.5 to 2.1)	1.2	(2.2 to 0.3)
	Unvaccinated group	11.0	(15.0 to 7.9)	9.0	(12.6 to 6.4)	9.3	(12.8 to 6.5)	4.3	(6.1 to 2.9)
	% Difference	-42.9%	(-8.9% to -66.1%)	-54.3%	(-23.7% to -73.9%)	-61.2%	(-31.3% to -78.9%)	-72.5%	(-41.9% to -93.0%)
Rate of COVID-19 hospital admissions	Vaccinated group	8.6	(11.4 to 6.3)	6.7	(9.4 to 4.6)	4.8	(6.8 to 3.2)	1.6	(2.7 to 0.6)
	Unvaccinated group	13.4	(17.6 to 9.9)	13.1	(17.6 to 9.6)	11.6	(14.9 to 8.4)	6.4	(8.5 to 4.5)
	% Difference	-35.5%	(-1.2% to -58.1%)	-49.2%	(-21.1% to -68.5%)	-58.4%	(-33.1% to -73.9%)	-75.1%	(-51.9% to -90.4%)
Controls aged 72 - 75 years excluding those vaccinated before 14 days of the end of the monitoring period									
Cohort	Size (% Match Rate)	80.7%		80.6%		80.5%		79.6%	
Rate of positive COVID-19 tests	Vaccinated group	28.9	(34.8 to 23.9)	15.0	(18.3 to 11.8)	9.4	(11.8 to 7.2)	5.4	(6.9 to 4.0)
	Unvaccinated group	40.2	(47.4 to 33.4)	31.0	(37.6 to 25.7)	20.9	(25.7 to 16.6)	16.5	(20.9 to 13.1)
	% Difference	-28.1%	(-6.5% to -44.7%)	-51.7%	(-36.1% to -64.5%)	-55.1%	(-37.2% to -68.5%)	-67.3%	(-54.0% to -77.4%)
Rate of COVID-19 realated A&E attendances	Vaccinated group	9.2	(12.3 to 6.7)	5.6	(8.0 to 3.8)	4.1	(5.8 to 2.8)	2.0	(3.1 to 1.2)
	Unvaccinated group	10.9	(15.3 to 7.3)	11.2	(15.9 to 7.2)	9.2	(12.8 to 6.2)	7.3	(11.2 to 4.0)
	% Difference	-15.6%	(38.3% to -44.9%)	-49.5%	(-16.0% to -70.4%)	-55.6%	(-26.4% to -73.9%)	-71.9%	(-42.0% to -85.7%)
Rate of COVID-19 related hospital admissions via A&E	Vaccinated group	6.4	(8.8 to 4.4)	4.3	(6.2 to 2.8)	3.2	(4.7 to 2.0)	1.6	(2.6 to 0.9)
	Unvaccinated group	7.3	(10.8 to 4.2)	7.7	(11.3 to 4.6)	6.2	(9.1 to 3.9)	5.5	(8.3 to 2.9)
	% Difference	-12.0%	(70.1% to -47.8%)	-43.9%	(8.5% to -69.6%)	-48.5%	(-6.5% to -71.9%)	-70.1%	(-36.6% to -86.5%)
Rate of COVID-19 hospital admissions	Vaccinated group	9.6	(12.8 to 7.0)	6.6	(8.7 to 4.6)	3.9	(5.5 to 2.5)	1.9	(2.8 to 1.1)
	Unvaccinated group	9.0	(13.9 to 5.4)	10.2	(14.6 to 6.3)	6.9	(11.0 to 4.3)	7.0	(10.3 to 4.2)
	% Difference	6.3%	(101.5% to -36.9%)	-35.6%	(11.4% to -60.2%)	-43.4%	(2.0% to -68.1%)	-73.3%	(-50.8% to -86.1%)
Controls aged 72 - 75 years excluding those vaccinated before the end of the monitoring period									
Cohort	Size (% Match Rate)	80.4%		79.6%		77.7%		70.9%	
Rate of positive COVID-19 tests	Vaccinated group	28.6	(34.8 to 23.2)	14.8	(18.0 to 11.8)	9.2	(11.7 to 7.1)	5.5	(7.3 to 3.9)
	Unvaccinated group	38.8	(45.6 to 32.6)	29.5	(34.9 to 24.9)	20.7	(25.1 to 16.7)	14.9	(17.7 to 12.2)
	% Difference	-26.2%	(-4.7% to -43.8%)	-49.7%	(-34.8% to -61.8%)	-55.6%	(-38.5% to -67.5%)	-62.8%	(-49.3% to -74.4%)
Rate of COVID-19 realated A&E attendances	Vaccinated group	8.9	(11.7 to 6.4)	5.2	(7.1 to 3.6)	3.5	(5.1 to 2.3)	2.0	(3.0 to 1.1)
	Unvaccinated group	10.4	(15.7 to 6.6)	10.4	(15.0 to 6.6)	7.6	(11.1 to 4.6)	6.4	(9.5 to 4.1)
	% Difference	-13.9%	(44.2% to -49.3%)	-49.9%	(-14.7% to -70.%)	-53.3%	(-19.5% to -73.8%)	-69.4%	(-41.8% to -85.7%)
Rate of COVID-19 related hospital admissions via A&E	Vaccinated group	6.3	(8.8 to 4.2)	4.0	(5.8 to 2.6)	2.9	(4.3 to 1.8)	1.5	(2.6 to 0.7)
	Unvaccinated group	6.9	(10.6 to 4.2)	7.5	(11.0 to 4.6)	5.4	(8.2 to 3.3)	4.8	(7.3 to 3.0)
	% Difference	-8.6%	(64.6% to -45.7%)	-46.1%	(2.9% to -68.4%)	-46.3%	(5.0% to -72.4%)	-69.5%	(-35.6% to -85.0%)
Rate of COVID-19 hospital admissions	Vaccinated group	9.6	(12.7 to 6.9)	6.2	(8.5 to 4.3)	3.7	(5.2 to 2.4)	1.8	(3.0 to 1.0)
	Unvaccinated group	9.9	(14.4 to 6.5)	10.5	(15.0 to 6.9)	7.4	(11.0 to 4.5)	6.8	(9.7 to 4.5)
	% Difference	-3.1%	(65.0% to -43.4%)	-41.1%	(-3.1% to -64.8%)	-49.6%	(-7.6% to -71.9%)	-73.7%	(-50.0% to -87.3%)

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