Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study)

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ABSTRACT

Background

BNT162b2 mRNA and ChAdOx1 nCOV-19 adenoviral vector vaccines have been rapidly rolled out in the UK. We determined the factors associated with vaccine coverage for both vaccines and documented the vaccine effectiveness of the BNT162b2 mRNA vaccine in our healthcare worker (HCW) cohort study of staff undergoing regular asymptomatic testing.

Methods

The SIREN study is a prospective cohort study among staff working in publicly funded hospitals. Baseline risk factors, vaccination status (from 8/12/2020-5/2/2021), and symptoms are recorded at 2 weekly intervals and all SARS-CoV-2 polymerase chain reaction (PCR) and antibody test results documented. A mixed effect proportional hazards frailty model using a Poisson distribution was used to calculate hazard ratios to compare time to infection in unvaccinated and vaccinated participants to estimate the impact of the BNT162b2 vaccine on all (asymptomatic and symptomatic) infection.

Findings

Vaccine coverage was 89% on 5/2/2021. Significantly lower coverage was associated with prior infection (aOR 0.59 95% confidence interval [CI] 0.54-0.64), female (aOR 0.72, 95% CI 0.63-0.82), aged under 35 years, being from minority ethnic groups (especially Black, aOR 0.26, 95% CI 0.21-0.32), porters/security guards (aOR 0.61, 95% CI 0.42-0.90),or midwife (aOR 0.74, 95% CI 0.57-0.97), and living in more deprived neighbourhoods (IMD 1 (most) vs. 5 (least) (aOR 0.75, 95% CI 0.65-0.87). A single dose of BNT162b2 vaccine demonstrated vaccine effectiveness of 72% (95% CI 58-86) 21 days after first dose and 86% (95% CI 76-97) seven days after two doses in the antibody negative cohort.

Conclusion

Our study demonstrates that the BNT162b2 vaccine effectively prevents both symptomatic and asymptomatic infection in working age adults; this cohort was vaccinated when the

dominant variant in circulation was B1.1.7 and demonstrates effectiveness against this variant.

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and medRxiv for studies including “asymptomatic” and “symptomatic” SARS-CoV-2 results after vaccination. Only a single paper existed for ChAdOx1 which stated that it reduced all (symptomatic or asymptomatic) infection by 51.9% (95% CI 42.0-60.1%). Three studies from Israel demonstrated that those who attended symptomatic testing had reduced infections two weeks post vaccination; a single healthcare worker cohort study in Israel, demonstrated vaccine effectiveness of 75% (95% CI 72 – 84%) from 15 to 28 days following the first dose of the BNT162b2 vaccine to reduce symptomatic infection. No data on asymptomatic infection through routinely collected swabs asymptomatic testing was available for the BNT162b2 vaccine.

Added value of this study

This is a large established cohort study in HCWs that enables accurate measurement of asymptomatic and symptomatic infection rates in the vaccinated and unvaccinated population.

It measures the impact of a single dose of vaccine over the first 8-week period. We have estimated the vaccine effectiveness against all (symptomatic and asymptomatic) infection for the BNT162b2 vaccine to be at least 70% 21 days after the first dose, which increased to at least 85% seven days after the second dose.

It also highlights the vaccine coverage and uptake among hospital staff. Further engagement is required in groups that have not yet accepted the vaccine offer.

Implications of all the available evidence

We provide strong evidence that vaccinating working age adults will substantially reduce asymptomatic and symptomatic SARS-CoV-2 infection and therefore reduce transmission of infection in the population. However, it does not eliminate infection risk completely and

85 therefore personal protective equipment, non-pharmaceutical interventions and regular
86 asymptomatic testing will need to be continued until prevalence of SARS-CoV-2 is extremely
87 low to reduce the risk of transmission in healthcare settings.

INTRODUCTION

Since the World Health Organization (WHO) declared the emergence of Coronavirus Disease 2019 (COVID-19) a pandemic on 11 March 2020, over 2.4 million people have died around the world [1], including over 120,000 people in the United Kingdom (UK) [2]. There has been an unprecedented international effort by private and public institutions to develop a vaccine against its causative agent, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[3] In less than a year, three COVID-19 vaccine candidates have been granted Emergency Use Authorization by the UK Medicines and Healthcare products Regulatory Agency (MHRA),[4] with several more in the development pipeline. The BNT162b2 mRNA (Pfizer-BioNTech) and ChAdOx1 nCoV-19 adenoviral (Oxford AstraZeneca COVID-19) vaccines, were approved on 2 December and 30 December 2020 respectively, based on interim analyses from phase 3 Randomized Controlled Trials (RCT)[6, 7],[5,6] and were deployed for use within seven days of authorisation.

Following advice from the Joint Committee on Vaccination and Immunisation (JCVI), the UK Government selected a vaccination strategy with the aim of rapidly reducing hospitalisations, severe outcomes and preventable deaths from COVID-19.[7] The initial phase targeted individuals at high-risk of severe COVID-19, such as care home residents and their carers, people aged 80 years and over, and frontline HCWs, recognising this group's particular high exposure and potential role in transmission. On 30 December, the JCVI published their recommendation to delay the 2nd dose of the deployed coronavirus vaccines by up to 12 weeks with the aim of optimising the public health impact of the vaccination campaign in the population by doubling the number of people who would receive the first dose.[8] By 19 February 2021, the UK had vaccinated more than 17.2 million people (25% of the population).[9] However, population-level vaccine effectiveness studies are needed to assess the impact of coronavirus vaccination in the real world and inform developments of the public health policy.

The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) Study is a large, multi-centre prospective cohort study of HCWs and support staff in publicly funded (National Health Service (NHS) hospitals in the United Kingdom.[10] SIREN initially investigated the effect of prior infection on protection against re-infection and was amended to investigate COVID-19 vaccine effectiveness in January 2021.

In this study, we aimed to describe the factors associated with both BNT162b2 and ChAdOx1 nCoV-19 vaccine coverage and early vaccine effectiveness of BNT162b2 vaccine against all (asymptomatic and symptomatic) infection in this large-scale cohort of HCWs in England.

METHODS

Study design and setting

The SIREN study is a prospective cohort study among staff working in the publicly funded hospitals (NHS) across the UK. The SIREN protocol is described elsewhere.[11]

Participants

HCWs, support staff and administrative staff working at hospital sites participating in SIREN, who could provide informed consent and anticipated remaining engaged in follow-up for 12 months were eligible to join SIREN. Participants were excluded from this analysis if they enrolled after 7 December 2020, had no PCR tests after 7 December 2020, or had insufficient PCR and antibody data to complete cohort assignment.

Variables

The primary outcome variable for the vaccine coverage analysis was the binary 'ever vaccinated' variable. Participants were categorised as 'ever vaccinated' if they had at least one vaccine dose recorded from 8 December 2020 to 5 February 2021 from at least one of the two vaccination data sources available. Data on vaccination date, manufacturer and batch

number was available for each dose. Second doses were excluded if they preceded the first dose and marked as 'short interval' if they were less than 19 days after the first dose.

The primary outcome variable for the vaccine effectiveness analysis was a PCR confirmed SARS-CoV-2 infection. This was defined as a new PCR positive result during follow-up for the negative cohort and a reinfection during the follow-up in the positive cohort, irrespective of symptom status.[10] Participants were assigned into either the positive cohort (antibody positive or history of infection (prior antibody or PCR positive)) or the negative cohort (antibody negative with no prior positive test) at the beginning of the follow up period (7 December 2020).

Data sources and measurement

Vaccination data was obtained directly from participants completing the enrolment and follow-up questionnaires and from linkage on personal identifiable information (NHS number, surname, date of birth and postcode) to the National Immunisation Management System (NIMS), the registry of COVID-19 vaccination in England.

SIREN participants undergo fortnightly asymptomatic PCR testing (anterior nasal swabs or combined nose and oropharyngeal swabs) and monthly antibody testing at their site of enrolment. In addition, hospitals introduced twice weekly asymptomatic testing using a lateral flow device (LFD), Innova SARS-CoV-2 Antigen Rapid Qualitative Test (Innova), to all frontline HCWs for twice weekly asymptomatic testing in November 2020. All positive LFD tests were confirmed by PCR. Participants consent for the release of all SARS-CoV-2 PCR and antibody test results before or after enrolment to the study team through the Public Health England (PHE) national laboratory testing surveillance system. The SIREN SQL database runs automated data linkage with the laboratory surveillance system daily to extract new positive and negative test results.

Participants are requested to complete online questionnaires at enrolment and fortnightly intervals, capturing data on demographics, symptoms, testing and exposures (household, community and occupational). Index of Multiple Deprivation a measure of neighbourhood relative deprivation, calculated by the Office of National Statistics, was obtained through linkage on participant postcode.

Data was extracted from all sources on 08 February 2021.

Bias reduction

Data were collected on potential confounders, including site and participant demographics to enable adjusted analysis. Analysis was restricted to one manufacturer only, where sufficient follow-up time had accrued; data was truncated on participants with an unreliable date of second dose (<19 days). Sample date of a PCR positive result was used as the event date which may have introduced some misclassification of vaccination status relative to infection or onset in the period shortly after vaccination and informed our decision to calculate cumulative vaccine effectiveness after suitable intervals (21 days post first dose and 7 days post second dose), in order to focus on infections acquired since vaccination after a sufficient interval for biological protection.

Study size

Prior to vaccine introduction calculations of the precision of effectiveness estimates were performed on an estimated cohort size of 40,000, 65% seronegative at baseline, coverage averaging at 75% in the follow-up period, and incidence in the follow-up period ranging from 0.5% to 5%. Precision estimates around effectiveness of 60% and 90% gave 95% confidence intervals ranging from the widest for a VE of 60% (95%CI: 39-74) to the narrowest for a VE of 90% (95%CI: 88-92).

Person time at risk

Follow-up time for all participants started on 7 December 2020, the day before vaccine roll-out began, with all participants contributing at least one day of follow-up unvaccinated. Participants moved from unvaccinated to vaccinated within their assigned cohort on the date of the first vaccination dose. Participants contributed person-time to follow-up until either an event of interest (i.e. a new PCR positive in the negative cohort or a reinfection in the positive cohort); the date of the suspect second dose for those with an unreliable date of second dose; the date of their first dose for those vaccinated with the ChAdOx1 vaccine; or the censored date. We defined the end of follow-up in those who were not positive cases as the date of a negative test or 05 February 2021 if the test was after this date, in order to avoid immortal time bias. As symptomatic testing was done at any time of symptoms the most recent days could be biased towards symptomatic testing, therefore, the end of follow-up was defined at a date two days prior to the last date samples were available.

Statistical methods

Investigation of factors associated with vaccination was conducted using mixed effect multivariable logistic regression model (with hospital site as a random effect) to investigate confounding between demographic and occupational risk factors on the outcome variable 'ever vaccinated'. A backwards stepwise approach was used, removing variables from the model sequentially with those with the least effect at univariable analysis removed first, and goodness of fit was tested (likelihood ratio tests) after each change. Only the variables which demonstrated strong evidence of association on vaccine coverage were retained in the final model.

A mixed effect proportional hazards frailty model using a Poisson distribution was used to calculate Hazard Ratios to compare time to infection in unvaccinated and vaccinated participants to estimate the impact of the BNT162b2 vaccine on infection (including asymptomatic and symptomatic as the primary outcome). As the main covariate of interest (vaccination) changes as time elapses and the effect of vaccine changes over follow-up time,

we grouped time to infection into 12 vaccine intervals to analyse the short-term dynamics of post vaccination protection in detail. The models were fitted by Poisson regression with a log link, using COVID-19 infection as response, log of exposure times as an offset and dummies for the time intervals as explanatory variables to allow for different piecewise constant hazards.[12] The model fitting approach also provided estimates of the baseline hazard rates. The hospital site was added into models as a random effect to account for the extra variation and associated correlation that was not explained by risk/covariates variables. The frailty model was also extended by including individual within the site as an addition random effect. The results (not reported here) did not support heterogeneity among individuals after controlling for site effect and therefore our final model does not include individual. The fixed covariates included in the model were age, ethnicity, comorbidities, region, job role, frequency of COVID-19 patient contact, patient-facing role, workplace setting. Hazard ratios from 21 days after first dose and seven days after second dose were calculated using a weighted average method, the point at which an immunological response to the vaccine dose should have been provoked. Vaccine effectiveness was calculated as 1 – adjusted Hazard Ratio (vaccinated versus unvaccinated).

Three models were run on different cohorts within the study population. The main model included the full study population and adjusted for cohort assignment. Models were then run on the two cohorts separately, to provide estimates of vaccine effectiveness in the susceptible population (negative cohort) and the positive cohort with natural immunity following prior SARS-CoV-2 infection.

Ethics

The study was approved by the Berkshire Research Ethics Committee, Health Research Authority (IRAS ID 284460, REC reference 20/SC/0230) on 22 May 2020; the vaccine amendment was approved on 12/1/2021. The study is registered with ISRCTN (Trial ID: ISRCTN11041050).

Reporting

The study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines and the checklists are included in the Supplementary Appendix.[13]

RESULTS

Characteristics of participants included in the analysis

By 7 December 2020, 29,378 participants were enrolled and maintained in SIREN for the England cohort; 23,324 met the inclusion criteria and were included in this analysis from 104 hospitals[1]. At the start date of follow-up (7 December 2020), 8,203 (35%) participants were assigned to the positive cohort (antibody positive or had a previous antibody or PCR positive test) and 15,121 (65%) were assigned to the negative cohort.

Most participants were female (84%; 19,692), of white ethnicity (89%; 20,424), in a patient-facing role (86%; 20,054) and in a clinical discipline (66%; 15,502). A quarter (26%; n=5,874) of participants had a reported medical condition; with asthma (n=2,893), obesity (n=1,988) and diabetes (n=677) the most frequent.

The total follow-up time in this analysis was two calendar months and 1,106,905 participant person-days, 710,587 person-days unvaccinated and 396,318 person-days vaccinated. Participants were followed-up for a maximum of 59 days post first dose (median 21, interquartile range: 13-31) and 39 days post second dose (median 23, interquartile range: 17-28). Total person-days of follow-up in the negative cohort was 711,135 and 395,770 in the positive cohort.

[1] Whilst recruitment of participants from Scotland and Northern Ireland began before 31/12/2020 their testing and vaccination data was not available for linkage by the study team at the time of this analysis, and therefore they were excluded. Recruitment of Welsh participants began in 2021.

Vaccine coverage with the SIREN cohort up to 5 February 2021

At least one dose of vaccine was administered to 20,641 (89%) participants by 5 February 2021; 94% (19,384) received the BNT162b2 vaccine and 6% (1,252) received the ChAdOx1 vaccine. Roll-out of the first dose of vaccine in this cohort peaked on 12 January 2021 (Figure 1). Two doses of vaccine were administered to a minority of participants (n=1,607, 8%) by 5 February 2021; 99.9% (n=1,605) received the BNT162b2 vaccine and 0.1% (n=2) received the ChAdOx1 vaccine. The median length of time between first dose and second dose was 23 days; IQR: 21-26 days; range 19-28.

Demographic, household and occupational factors associated with being vaccinated

A description of the demographic, household and occupational factors associated with being vaccinated, including the proportions vaccinated and odds ratios are presented in table 1. In multivariable analysis, after controlling for all other risk factors and given site, having a prior infection, gender, age, ethnicity, IMD score and staff group remained significantly associated with vaccine coverage. Participants were less likely to have been vaccinated if they had a prior infection (aOR 0.59, 95% CI 0.54-0.64), were female (aOR 0.72, 95% CI 0.63-0.82), were aged under 35 (aOR 0.78, 95% CI 0.64-0.96), were from Black, Asian or minority ethnic groups, especially if they were Black (aOR 0.26, 95% CI 0.21-0.32), lived in areas of higher deprivation (IMD 1 (most) vs. 5 (least) aOR 0.75 , 95% CI 0.65-0.87) or worked as a porter/security/estates (aOR 0.61, 95% CI 0.42-0.90) or midwife (aOR 0.74, 95% CI 0.57-0.97).

Vaccine effectiveness against infection

There were 977 new infections during 710,587 person days of follow-up in the unvaccinated group, an incidence density of 14 infections per 10,000 person days of follow-up (table 2). In the vaccinated group, 21 days after the first dose, there were 71 new infections (incidence density 8 per 10,000 person-days of follow-up) and nine new infections seven days after the second dose (incidence density of 4 per 10,000 person days of follow-up).

Classic COVID-19 symptoms (fever, cough, change/loss of taste or smell) were reported by 620 (63%) cases in the unvaccinated group 14-days before or after their positive test date; 139 (14%) had other symptoms[2]; 51 (5%) were asymptomatic; and 167 (17%) did not complete the symptom status questionnaire within 2 weeks of their PCR test date. In comparison, of the infections 21 days after first dose and seven days after second dose in the vaccinated group, 32 (40%) had classic COVID-19 symptoms, 13 (16%) had other symptoms, 10 (13%) were asymptomatic and 25 (31%) did not complete the symptom status questionnaire for the time period.

After controlling for the other risk factors, cohort and at a given site, vaccine effectiveness against infection 21 days after the first dose of BNT162b2 vaccine in the overall study population was 70% (95% CI 53-87%) and increased to 85% (95% 74-96%) seven days after the second dose (table 2). Protection was higher when the negative cohort was modelled separately, and after adjustment for the other risk factors and at a given site; vaccine effectiveness was72% (95% CI 58-86%) 21 days after first dose and 86% (95% 76-97%) 7 days after the second dose. There was insufficient information to separately model the positive cohort at this analysis timepoint. The overall model showed that the positive cohort already had 90% protection (95% CI 88-92%) compared to the negative cohort following their natural infection (supplementary material).

Figures 2a and 2b show the trends in vaccine effectiveness measured over short post-vaccination intervals in the full cohort and negative cohort; this demonstrated a reduced risk of infection in vaccinated individuals immediately (0-3 days) following the first dose; there

[2] Participants were recorded as having 'other symptoms' if they reported ANY of the following symptoms: shortness of breath, sore throat, runny nose, headache, muscle aches, extreme fatigue, diarrhoea, nausea or vomiting or small itchy red patches on fingers or toes, on the follow-up questionnaire with a symptom onset date within 14-days before or after the PCR positive sample date.

was no significant effect between days 4-9, with a significant protection from infection increasing from day 10 onwards, and plateauing after 21 days. Following the second dose a similar pattern is observed. The hazard ratios, adjusted and unadjusted for each time period post vaccination in the full cohort and the negative cohort are provided in Appendix A Tables 3a & 3b.

DISCUSSION

Our follow-up of this large cohort of over 23,000 HCWs, whose prior SARS-CoV-2 infection history is known for two months after vaccine roll-out provides unique real-world data on the short-term vaccine effectiveness of the BNT162b2 vaccine against both symptomatic and asymptomatic infection. The regular PCR-testing of participants, regardless of symptom status, allowed for the detection of asymptomatic infection, an important proxy for reduction in transmission. Two months after roll-out commenced, 89% of our cohort had received at least one dose of COVID-19 vaccine; 8% had received two doses. We detected modest variability in coverage, with lower coverage observed in participants with prior infection, from Black, Asian and minority ethnic backgrounds, and living in areas of higher deprivation. We estimated the vaccine effectiveness against infection for the BNT162b2 vaccine to be at least 70% 21 days after the first dose, increasing to at least 85% 7 days after the second dose in our study population. This demonstrates that the BNT162b2 is effective against the B1.1.7 variant given its predominance throughout the studyperiod.[14]

The high vaccine coverage in SIREN may not be generalisable to UK HCWs or the general population, as those who have self-selected to participate in a research study may not be representative of UK HCWs or the population more generally.

With fewer of the cohort vaccinated with the ChAdOx1 vaccine, and the later roll-out resulting in less follow-up time accrued, we are currently unable to investigate the effectiveness of the ChAdOx1 vaccine within this study.

The analysis is based on PCR positivity, which may miss infections depending on the timing of the infection relative to PCR testing or PCR sensitivity, which if differential by vaccination status may lead to overestimation of the vaccine effect against all infections. However, given our cohort, irrespective of vaccine status, attended fortnightly asymptomatic PCR testing within SIREN, and additionally many also underwent twice weekly LFD testing with PCR confirmation, we believe most infections during this period will have been detected. The cohort will also have regular serological testing and the effect of seroconversion to both the S assay (for vaccine) and N assay (for infection) will be estimated in the future.

Given the high vaccine coverage and small proportion of participants remaining unvaccinated, the characteristics and exposures of this group may become sufficiently different from the vaccinated cohort to undermine the validity of future analyses. However, given the short follow-up period for this analysis, with all participants contributing follow-up time to the unvaccinated group, we do not consider this would have introduced significant bias at this stage.

Speculation of high levels of HCW vaccine hesitancy are not supported in our cohort study, with almost 90% receiving at least one dose of vaccination within two months of roll-out.[15] High and rapid vaccine HCW coverage was also reported in two single-centre cohort studies in Israel, reporting 79% and 90% coverage six weeks after roll-out.[16,17] Slightly lower uptake of 65% was reported in a single UK trust which also reported similar disparities in vaccination coverage by ethnicity.[18] Our findings also indicated that age, gender and occupation were associated with coverage, confirming a systematic review of 11 studies including 9,000 participants, on the intention of healthcare workers HCW to accept the COVID-19 vaccine, which concluded that older age, male gender and being a doctor were factors associated with increased willingness to get vaccinated.[15] Conversely, the authors also found that people with prior SARS-CoV-2 infection or co-morbidities expressed more willingness to take the vaccine,

not seen in our data. We also observed a significant trend of lower COVID-19 vaccination coverage in those living in more deprived areas, corresponding to a population study of 23.4 million patients in the UK.[19]

Our analysis identified a reduced risk of infection in vaccinated individuals immediately (0-3 days) following the first dose, which cannot be plausibly explained by the immune response to the vaccine; this is likely a deferral effect bias where those that are symptomatic, currently PCR positive or have been recently exposed to a COVID-19 case may defer their vaccination and be under-represented in accordance with national guidance.[20]

We found a vaccine effectiveness, at a given site, of at least 70% overall (72% in the negative cohort) against both asymptomatic and symptomatic infection, from 21 days post-first dose of the BNT162b2 vaccine. This is comparable to a single-centre Israeli HCW cohort study vaccine effectiveness of 75% (95% CI 72 – 84), 15-28 days following first dose of BNT162b2 vaccine [16]. However, this study had no routine laboratory surveillance to pick up asymptomatic cases and only detected cases if symptomatic, whereas SIREN had regular asymptomatic testing; in addition, their adjustment for other potential risk factors was more limited.

Another population-level study in Israel reported a 51% reduction in PCR-confirmed SARS-CoV-2 infections 13-24 days after individuals received the first dose of BNT162b2 vaccine, compared to historical controls' 1-12 days [21]. This mirrors the 52.4% (95% CI: 29.5 - 68.4) vaccine efficacy estimated by Pfizer-BioNTech researchers, between the first and second dose.[6] Whilst follow up periods differed, the RCT included true controls and the Israeli study included PCR-positivity regardless of symptom status compared to symptomatic confirmed cases in the phase III BNT162b2 RCT. A preprint from researchers re-analysing the data from the Israeli study using daily incidence of infection, calculated a vaccine effectiveness of 91% at day 21 post-vaccination.[22] This estimate is closer to the 92.6% vaccine efficacy 14–21 days

after the first dose, calculated by researchers using data submitted by the manufacturers to the Food and Drug Administration from vaccine trials.[23]

The differences in the vaccine effectiveness estimates may be due to the differences in study design and populations included. Nonetheless, BNT162b2 is making a substantial impact in reducing SARS-CoV-2 infection rates in vaccinated populations. A study with a comparable methodology to SIREN, focussing on "Covid-19 Vaccine Effectiveness in Healthcare Personnel in Clalit Health Services in Israel", is currently underway [ClinicalTrials.gov number NCT04709003], but results are awaited. A notable difference is that people in Israel that have recovered from SARS-CoV-2 infection are not eligible for vaccination at present;[24] therefore, their population studies do not include the seropositive people that would be present in a general population. Weekly swabbing of a sub-set of asymptomatic and symptomatic participants was carried out in the Oxford-AstraZeneca RCT and investigators reported reduced viral load and PCR positivity in the COVID-19 vaccinated participants; a signal that transmission may be reduced by their vaccine.[25] This is the first study that describes the reduction in all cases of infection with BNT162b2.

Most data on vaccinated UK individuals are from people aged >75years old, where vaccine effectiveness may be lower due to immunosenesence.[27] The SIREN cohort is taken from working age people, making the conclusions more relevant for the overall adult population. However, the healthy worker effect bias may underestimate the disease impact compared to the general population.[28]

Further work on this cohort is underway including measuring the impact of vaccination on symptoms, serological responses, potential hospitalisations, and development of post-acute-COVID. We will attempt to sequence infections occurring at least 21 days post vaccination to determine proportion of novel variants.

This study clearly demonstrates that the vaccine does not prevent all cases of infection and therefore HCWs will need to continue to wear personal protective equipment while caring for all patients, observe physical distancing and other non-pharmaceutical measures in and outside work and continue to perform regular asymptomatic testing (especially as typical symptoms were reduced post vaccination) until COVID prevalence is considerably lower.

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The funder had no role in the data collection, analysis, interpretation or the decision to submit.

Trial Registration

IRAS ID 284460, REC reference 20/SC/0230 Berkshire Research Ethics Committee, Health Research Authority and Health and Care Research Wales approval granted 22 May 2020. Trial registered with ISRCTN, Trial ID: ISRCTN11041050.

https://www.isrctn.com/ISRCTN11041050

Author Contributions

SH conceived this study, commented on the draft protocol, supervised the study, drafted and edited the final manuscript. JLB, NA and VH wrote the first draft of the protocol and analysis plan for the vaccine effectiveness sub-study. SF and VH cleaned and analysed data. VH and BO performed the literature search and drafted the manuscript. AS performed the statistical modelling of VE supervised by NA and AC. All authors contributed to the study design. All authors contributed to drafting the protocol and revised the manuscript for important intellectual content. All authors gave final approval of the version to be published.

Conflict of interest statement

The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

Data sharing statement

The metadata will be available through the HDR-UK Co-Connect platform and available for secondary analysis once the study has completed reporting.

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Table 1: Characteristics of vaccinated and non-vaccinated SIREN participants and factors associated with vaccine coverage in multivariable logistic regression analysis, (n=23,324)

Characteristics		Not Vaccinated	Vaccinated	OR (95% CI)	p-value	aOR** (95% CI)	p-value
		n (%)	n (%)				
Prior COVID-19 infection*							
	Negative	1405 (9.3)	13716 (90.7)	Reference			
	Positive	1278 (15.6)	6925 (84.4)	0.56 (0.51-0.60)	<0.001	0.59 (0.54-0.64)	<0.001
Gender							
	Male	333 (9.2)	3270 (90.8)	Reference			
	Female	2346 (11.9)	17346 (88.1)	0.75 (0.67-0.85)	<0.001	0.72 (0.63-0.82)	<0.001
	Other	4 (13.8)	25 (86.2)	0.64 (0.22-1.84)	0.404	0.94 (0.30-2.93)	0.913
Age group							
	Under 25	136 (16.1)	711 (83.9)	Reference			
	25-34	886 (19.7)	3614 (80.3)	0.78 (0.64-0.95)	0.014	0.78 (0.64-0.96)	0.018
	35-44	650 (11.5)	4998 (88.5)	1.47 (1.20-1.80)	<0.001	1.45 (1.18-1.79)	<0.001
	45-54	600 (8.4)	6566 (91.6)	2.09 (1.71-2.56)	<0.001	2.22 (1.80-2.73)	<0.001
	55-64	382 (8.0)	4412 (92.0)	2.21 (1.79-2.73)	<0.001	2.31 (1.85-2.87)	<0.001
	Over 65	29 (7.9)	340 (92.1)	2.24 (1.47-3.42)	<0.001	2.19 (1.42-3.37)	<0.001
Ethnicity							
	White	2119 (10.4)	18305 (89.6)	Reference			
	Mixed Race	69 (19.4)	287 (80.6)	0.48 (0.37-0.63)	<0.001	0.56 (0.43-0.75)	<0.001
	Asian	250 (15.8)	1337 (84.2)	0.62 (0.54-0.71)	<0.001	0.65 (0.56-0.76)	<0.001
	Black	162 (34.9)	302 (65.1)	0.22 (0.18-0.26)	<0.001	0.26 (0.21-0.32)	<0.001
	Chinese	17 (12.7)	117 (87.3)	0.80 (0.48-1.33)	0.383	0.73 (0.43-1.25)	0.252
	Other ethnic group	56 (17.8)	258 (82.2)	0.53 (0.40-0.71)	<0.001	0.54 (0.39-0.73)	<0.001
	Prefer not to say	10 (22.2)	35 (77.8)	0.41 (0.20-0.82)	0.012	0.30 (0.14-0.65)	0.002
Pre-existing medical condition^							
	No medical condition	2060 (11.8)	15390 (88.2)	Reference			
	Immunosuppression	56 (11.7)	421 (88.3)	1.01 (0.76-1.33)	0.965	-	-

Chronic Respiratory conditions	305 (10.4)	2619 (89.6)	1.15 (1.01-1.31)	0.032	-	-
Chronic Non-Respiratory conditions	262 (10.6)	2211 (89.4)	1.13 (0.99-1.29)	0.079	-	-
Household size						
Just you	283 (12.1)	2063 (87.9)	Reference			
Two to four	2080 (11.2)	16494 (88.8)	1.09 (0.95-1.24)	0.213	-	-
Over four	297 (12.7)	2037 (87.3)	0.94 (0.79-1.12)	0.492	-	-
Prefer not to say	23 (32.9)	47 (67.1)	0.28 (0.17-0.47)	<0.001	-	-
Index of Multiple Deprivation						
5 (least deprived)	507 (9.0)	5107 (91.0)	Reference			
4	534 (9.7)	4947 (90.3)	0.92 (0.81-1.04)	0.199	1.02 (0.89-1.16)	0.795
3	591 (11.1)	4731 (88.9)	0.79 (0.70-0.90)	<0.001	0.92 (0.81-1.05)	0.216
2	577 (14.1)	3512 (85.9)	0.60 (0.53-0.69)	<0.001	0.78 (0.69-0.90)	<0.001
1 (most deprived)	436 (16.6)	2198 (83.4)	0.50 (0.44-0.57)	<0.001	0.75 (0.65-0.87)	<0.001
Not known	38 (20.7)	146 (79.3)	0.38 (0.26-0.55)	<0.001	0.53 (0.36-0.78)	0.001
Region						
Yorkshire and the Humber	239 (11.5)	1832 (88.5)	Reference			
East Midlands	248 (10.1)	2200 (89.9)	1.16 (0.96-1.40)	0.128	1.14 (0.80-1.62)	0.461
East of England	299 (10.8)	2462 (89.2)	1.07 (0.90-1.29)	0.437	1.12 (0.80-1.56)	0.505
London	444 (15.5)	2416 (84.5)	0.71 (0.60-0.84)	<0.001	1.00 (0.73-1.37)	1.000
North East	53 (9.7)	496 (90.3)	1.22 (0.89-1.67)	0.212	1.31 (0.76-2.26)	0.340
North West	350 (12.7)	2403 (87.3)	0.90 (0.75-1.07)	0.218	0.96 (0.70-1.32)	0.803
South East	247 (9.1)	2462 (90.9)	1.30 (1.08-1.57)	0.006	1.24 (0.91-1.71)	0.176
South West	464 (9.7)	4335 (90.3)	1.22 (1.03-1.44)	0.019	1.11 (0.82-1.49)	0.506
West Midlands	339 (14.3)	2035 (85.7)	0.78 (0.66-0.93)	0.007	0.87 (0.63-1.19)	0.380
Staff group						
Admin	377 (10.5)	3223 (89.5)	Reference			
Nursing/Healthcare Assistant	1275 (13.0)	8551 (87.0)	0.78 (0.69-0.89)	<0.001	0.96 (0.84-1.09)	0.515
Doctor	189 (7.5)	2332 (92.5)	1.44 (1.20-1.73)	<0.001	1.82 (1.49-2.22)	0.000
Midwife	88 (15.5)	478 (84.5)	0.64 (0.49-0.82)	<0.001	0.74 (0.57-0.97)	0.027
Specialist staff	156 (11)	1262 (89.0)	0.95 (0.78-1.15)	0.584	1.28 (1.04-1.57)	0.020
Estates/Porters/Security	38 (17.1)	184 (82.9)	0.57 (0.39-0.82)	0.002	0.61 (0.42-0.90)	0.012
Pharmacist	35 (10.0)	316 (90.0)	1.06 (0.73-1.52)	0.770	1.59 (1.09-2.33)	0.016

Healthcare Scientist	91 (11.1)	729 (88.9)	0.94 (0.74-1.19)	0.599	1.16 (0.90-1.49)	0.261
Other	434 (10.8)	3566 (89.1)	0.96 (0.83-1.11)	0.594	1.13 (0.97-1.31)	0.126
Occupation setting⁺						
Offices and laboratory (lower risk)	932 (11.2)	7384 (88.8)	Reference			
Patient facing non-clinical	112 (12.9)	757 (87.1)	0.85 (0.69-1.05)	0.138	-	-
Outpatient	469 (11.6)	3590 (88.4)	0.97 (0.86-1.09)	0.567	-	-
Inpatient wards and ambulance	498 (14)	3069 (86.0)	0.78 (0.69-0.87)	<0.001	-	-
Intensive Care (higher risk)	157 (13.0)	1053 (87.0)	0.85 (0.71-1.01)	0.071	-	-
Other	515 (9.7)	4788 (90.3)	1.17 (1.05-1.31)	0.006	-	-
Contact with patients or working in patient-facing areas						
No	330 (10.1)	2940 (89.9)	Reference			
Yes	2353 (11.7)	17701 (88.3)	0.84 (0.75-0.95)	0.006	-	-
Frequency of contact with COVID-19 patients in the workplace						
Never	793 (9.6)	7484 (90.4)	Reference			
Daily	871 (15.4)	4777 (84.6)	0.58 (0.52-0.64)	<0.001	-	-
Weekly	448 (10.8)	3688 (89.2)	0.87 (0.77-0.99)	0.029	-	-
Monthly	239 (11.3)	1883 (88.7)	0.83 (0.72-0.97)	0.021	-	-
Less than monthly	332 (10.6)	2809 (89.4)	0.90 (0.78-1.03)	0.113	-	-
All Participants	**2683 (11.5)**	**20641 (88.5)**				

*Ever antibody or PCR positive as of 07 December 2020; ^pre-existing medical condition categories: immunosuppression (cancers affecting the immune system in the last 5 years, rheumatological/autoimmune conditions and on immunosuppressive therapy, organ or bone marrow transplantation, asplenia), Chronic respiratory conditions (asthma, chronic respiratory disease), chronic non-respiratory conditions (diabetes, obesity, chronic heart disease, chronic kidney disease, chronic liver disease, other cancers, dementia, other neurological disorder and HIV) and no reported medical conditions. Where participants reported multiple conditions, they were assigned to a category dependent on which condition was considered by the study team to be the most severe.
⁺Occupation setting: 1 = office, laboratory, estates; 2: community pharmacy, hospital pharmacy, communal areas open to the public, mobile across areas (porters); 3: outpatient, radiology, day ward, general practice, renal dialysis unit; 4: inpatient ward, theatres, emergency department, maternity unit/labour ward, ambulance; 5: intensive care; Other
**multivariable model included and adjusted for: site (as a random effect), and fixed effects: prior infection status, age, gender, ethnicity, IMD, region and staff group

Table 2: Effectiveness of the BNT162b2 COVID-19 vaccine against infection in SIREN participants, stratified by cohort, between 7 December 2020 and 5 February 2021, (n=23,324)

Vaccine group	Total person time (days)	Number of PCR positives	Incidence Density per 10,000 person days	Unadjusted Hazard Ratio (95% CI)^	Adjusted Hazard Ratio (95% CI)*
Full cohort					
Unvaccinated	710587	977	14	Reference	Reference
d1 ≥21	87278	71	8	0.43 (0.23-0.64)	0.30 (0.15-0.45)
d2 ≥7	20978	9	4	0.23 (0.06-0.40)	0.15 (0.04-0.26)
Negative cohort					
Unvaccinated	442605	902	20	Reference	Reference
d1 ≥21	59748	66	11	0.33 (0.17-0.49)	0.28 (0.14-0.42)
d2 ≥7	14746	8	5	0.18 (0.04-0.31)	0.14 (0.03-0.24)
Positive cohort**					
Unvaccinated	267982	75	3	-	-
d1 ≥21	27530	5	2	-	-
d2 ≥7	6232	1	2	-	-

^Unadjusted includes vaccine effect (period) only; *the full model was adjusted for site as a random effect, period, and fixed effects: age, gender, ethnicity, comorbidities, job role, frequency of contact with COVID-19 patients, employed in a patient facing role, occupational exposure. **there was insufficient information to model the positive cohort separately so stratified hazard ratios are not available for the positive cohort.

FIGURES

Figure 1: Number of vaccinated SIREN participants by dose, manufacturer and day, 8 December 2020 to 5 February 2021 (n=20,641)

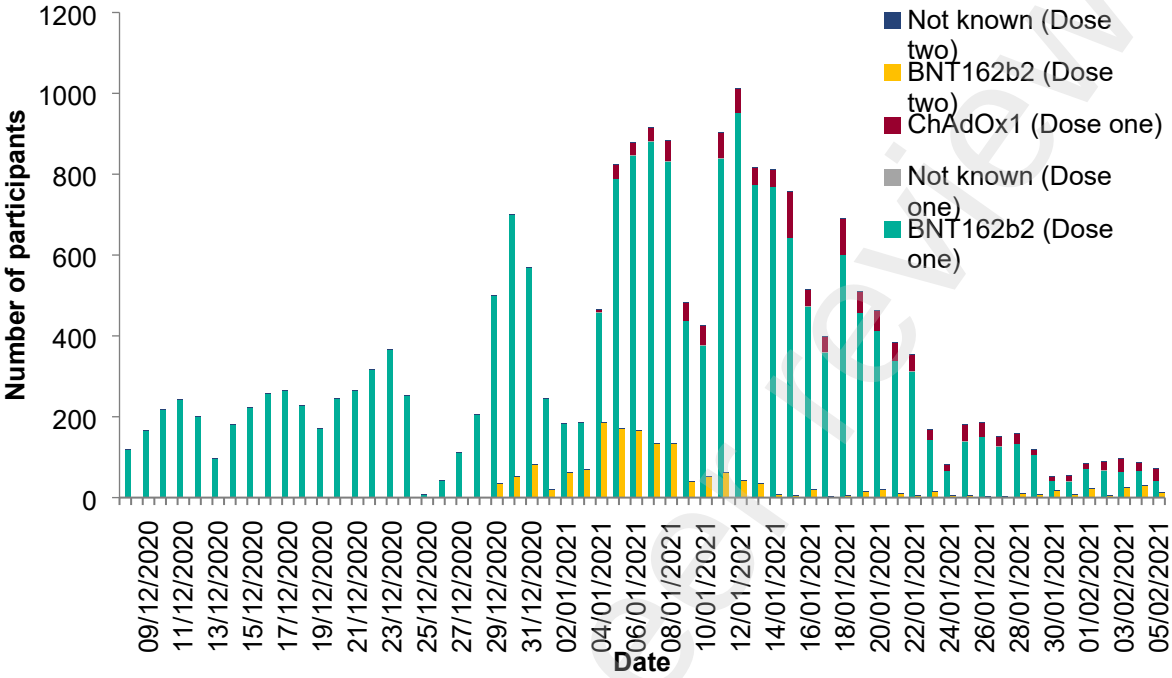

Figure 2a: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, full cohort (n=23,324)

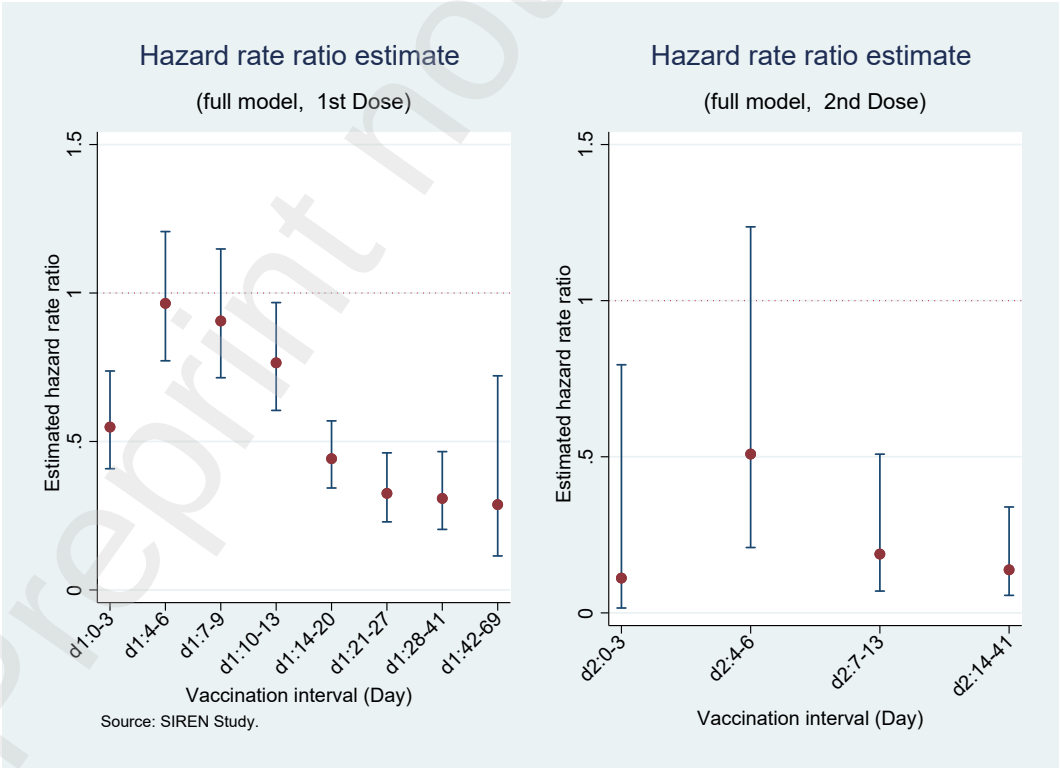

Figure 2b: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, negative cohort (n=15,121)