1   **Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine**

2   **coverage in healthcare workers in England, multicentre prospective cohort study (the**

3   **SIREN study)**

4

5   **Authors:**

6   Hall V FFPH[1,2], Foulkes S MSc[1], Saei A PhD[1], Andrews N PhD[1,5], Oguti B[1,3], Charlett A

7   PhD[1,4,5], Wellington E MSc[1], Stowe J PhD[1], Gillson N BA[1], Atti A MSc[1], Islam J PhD[1],

8   Karagiannis I PhD[1], Munro K MSc[1], Khawam J BSc[1], The SIREN Study Group∞, Chand MA

9   FRCPath[1,6], Brown CS FRCPath[1], Ramsay M FFPH[1,5], Lopez-Bernal J PhD[1], Hopkins S

10   FRCPath[1,2]*.

11

12   *Corresponding author*: *PHE Colindale, 61 Colindale Avenue, London NW9 5EQ.*

13   *susan.hopkins@phe.gov.uk*

14

15   SIREN study group∞ contributors listed in attached file

16   Author affiliations:

17   1. Public Health England Colindale;

18   2. The National Institute for Health Research Health Protection Research (NIHR) Unit in

19   Healthcare Associated Infections and Antimicrobial Resistance at the University of

20   Oxford, Oxford, UK.

21   3. Oxford Vaccine Group, University of Oxford

22   4. NIHR Health Protection Research Unit in Behavioural Science and Evaluation at

23   University of Bristol in partnership with Public Health England.

24   5. NIHR Health Protection Research Unit in Immunisation at the London School of

25   Hygiene and Tropical Medicine in partnership with Public Health England.

26   6. St Guys and Thomas's Hospital NHS Trust

27

28 **ABSTRACT**

29 **Background**

30 BNT162b2 mRNA and ChAdOx1 nCOV-19 adenoviral vector vaccines have been rapidly

31 rolled out in the UK. We determined the factors associated with vaccine coverage for both

32 vaccines and documented the vaccine effectiveness of the BNT162b2 mRNA vaccine in our

33 healthcare worker (HCW) cohort study of staff undergoing regular asymptomatic testing.

34 **Methods**

35 The SIREN study is a prospective cohort study among staff working in publicly funded

36 hospitals. Baseline risk factors, vaccination status (from 8/12/2020-5/2/2021), and symptoms

37 are recorded at 2 weekly intervals and all SARS-CoV-2 polymerase chain reaction (PCR)

38 and antibody test results documented. A mixed effect proportional hazards frailty model

39 using a Poisson distribution was used to calculate hazard ratios to compare time to infection

40 in unvaccinated and vaccinated participants to estimate the impact of the BNT162b2 vaccine

41 on all (asymptomatic and symptomatic) infection.

42 **Findings**

43 Vaccine coverage was 89% on 5/2/2021. Significantly lower coverage was associated with

44 prior infection (aOR 0.59 95% confidence interval [CI] 0.54-0.64), female (aOR 0.72, 95% CI

45 0.63-0.82), aged under 35 years, being from minority ethnic groups (especially Black, aOR

46 0.26, 95% CI 0.21-0.32), porters/security guards (aOR 0.61, 95% CI 0.42-0.90),or midwife

47 (aOR 0.74, 95% CI 0.57-0.97), and living in more deprived neighbourhoods (IMD 1 (most) vs.

48 5 (least) (aOR 0.75, 95% CI 0.65-0.87). A single dose of BNT162b2 vaccine demonstrated

49 vaccine effectiveness of 72% (95% CI 58-86) 21 days after first dose and 86% (95% CI 76-

50 97) seven days after two doses in the antibody negative cohort.

51 **Conclusion**

52 Our study demonstrates that the BNT162b2 vaccine effectively prevents both symptomatic

53 and asymptomatic infection in working age adults; this cohort was vaccinated when the

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

55   variant.

56   **Funding:** Public Health England and the Department of Health and Social Care; NIHR

57

58

60   **RESEARCH IN CONTEXT**

61   **Evidence before this study**

62   We searched PubMed and medRxiv for studies including "asymptomatic" and "symptomatic"

63   SARS-CoV-2 results after vaccination. Only a single paper existed for ChAdOx1 which

64   stated that it reduced all (symptomatic or asymptomatic) infection by 51.9% (95% CI 42.0-

65   60.1%). Three studies from Israel demonstrated that those who attended symptomatic

66   testing had reduced infections two weeks post vaccination; a single healthcare worker

67   cohort study in Israel, demonstrated vaccine effectiveness of 75% (95% CI 72 – 84%) from

68   15 to 28 days following the first dose of the BNT162b2 vaccine to reduce symptomatic

69   infection. No data on asymptomatic infection through routinely collected swabs

70   asymptomatic testing was available for the BNT162b2 vaccine.

71   **Added value of this study**

72   This is a large established cohort study in HCWs that enables accurate measurement of

73   asymptomatic and symptomatic infection rates in the vaccinated and unvaccinated

74   population.

75   It measures the impact of a single dose of vaccine over the first 8-week period. We have

76   estimated the vaccine effectiveness against all (symptomatic and asymptomatic) infection for

77   the BNT162b2 vaccine to be at least 70% 21 days after the first dose, which increased to at

78   least 85% seven days after the second dose.

79   It also highlights the vaccine coverage and uptake among hospital staff. Further

80   engagement is required in groups that have not yet accepted the vaccine offer.

81   **Implications of all the available evidence**

82   We provide strong evidence that vaccinating working age adults will substantially reduce

83   asymptomatic and symptomatic SARS-CoV-2 infection and therefore reduce transmission of

84   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.

88 **INTRODUCTION**

89 Since the World Health Organization (WHO) declared the emergence of Coronavirus Disease

90 2019 (COVID-19) a pandemic on 11 March 2020, over 2.4 million people have died around

91 the world [1], including over 120,000 people in the United Kingdom (UK) [2]. There has been an

92 unprecedented international effort by private and public institutions to develop a vaccine

93 against its causative agent, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-

94 CoV-2).[3] In less than a year, three COVID-19 vaccine candidates have been granted

95 Emergency Use Authorization by the UK Medicines and Healthcare products Regulatory

96 Agency (MHRA),[4] with several more in the development pipeline. The BNT162b2 mRNA

97 (Pfizer-BioNTech) and ChAdOx1 nCoV-19 adenoviral (Oxford AstraZeneca COVID-19)

98 vaccines, were approved on 2 December and 30 December 2020 respectively, based on

99 interim analyses from phase 3 Randomized Controlled Trials (RCT)[6, 7],[5,6] and were deployed

100 for use within seven days of authorisation.

101

102 Following advice from the Joint Committee on Vaccination and Immunisation (JCVI), the UK

103 Government selected a vaccination strategy with the aim of rapidly reducing hospitalisations,

104 severe outcomes and preventable deaths from COVID-19.[7] The initial phase targeted

105 individuals at high-risk of severe COVID-19, such as care home residents and their carers,

106 people aged 80 years and over, and frontline HCWs, recognising this group's particular high

107 exposure and potential role in transmission. On 30 December, the JCVI published their

108 recommendation to delay the 2nd dose of the deployed coronavirus vaccines by up to 12 weeks

109 with the aim of optimising the public health impact of the vaccination campaign   in the

110 population by doubling the number of people who would receive the first dose.[8] By 19

111 February 2021, the UK had vaccinated more than 17.2 million people (25% of the population).[9]

112 However, population-level vaccine effectiveness studies are needed to assess the impact of

113 coronavirus vaccination in the real world and inform developments of the public health policy.

114

115   The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) Study is a large, multi-centre

116   prospective cohort study of HCWs and support staff in publicly funded (National Health Service

117   (NHS) hospitals in the United Kingdom.[10] SIREN initially investigated the effect of prior

118   infection on protection against re-infection and was amended to investigate COVID-19 vaccine

119   effectiveness in January 2021.

120

121   In this study, we aimed to describe the factors associated with both BNT162b2 and ChAdOx1

122   nCoV-19 vaccine coverage and early vaccine effectiveness of BNT162b2 vaccine against all

123   (asymptomatic and symptomatic) infection in this large-scale cohort of HCWs in England.

124

125   **METHODS**

126   **Study design and setting**

127   The SIREN study is a prospective cohort study among staff working in the publicly funded

128   hospitals (NHS) across the UK. The SIREN protocol is described elsewhere.[11]

129

130   **Participants**

131   HCWs, support staff and administrative staff working at hospital sites participating in SIREN,

132   who could provide informed consent and anticipated remaining engaged in follow-up for 12

133   months were eligible to join SIREN.   Participants were excluded from this analysis if they

134   enrolled after 7 December 2020, had no PCR tests after 7 December 2020, or had insufficient

135   PCR and antibody data to complete cohort assignment.

136

137   **Variables**

138   The primary outcome variable for the vaccine coverage analysis was the binary 'ever

139   vaccinated' variable. Participants were categorised as 'ever vaccinated' if they had at least

140   one vaccine dose recorded from 8 December 2020 to 5 February 2021 from at least one of

141   the two vaccination data sources available. Data on vaccination date, manufacturer and batch

142　number was available for each dose. Second doses were excluded if they preceded the first

143　dose and marked as 'short interval' if they were less than 19 days after the first dose.

144

145　The primary outcome variable for the vaccine effectiveness analysis was a PCR confirmed

146　SARS-CoV-2 infection. This was defined as a new PCR positive result during follow-up for

147　the negative cohort and a reinfection during the follow-up in the positive cohort, irrespective of

148　symptom status.[10] Participants were assigned into either the positive cohort (antibody positive

149　or history of infection (prior antibody or PCR positive)) or the negative cohort (antibody

150　negative with no prior positive test) at the beginning of the follow up period (7 December 2020).

151

152　**Data sources and measurement**

153　Vaccination data was obtained directly from participants completing the enrolment and follow-

154　up questionnaires and from linkage on personal identifiable information (NHS number,

155　surname, date of birth and postcode) to the National Immunisation Management System

156　(NIMS), the registry of COVID-19 vaccination in England.

157

158　SIREN participants undergo fortnightly asymptomatic PCR testing (anterior nasal swabs or

159　combined nose and oropharyngeal swabs) and monthly antibody testing at their site of

160　enrolment. In addition, hospitals introduced twice weekly asymptomatic testing using a lateral

161　flow device (LFD), Innova SARS-CoV-2 Antigen Rapid Qualitative Test (Innova), to all frontline

162　HCWs for twice weekly asymptomatic testing in November 2020. All positive LFD tests were

163　confirmed by PCR. Participants consent for the release of all SARS-CoV-2 PCR and antibody

164　test results before or after enrolment to the study team through the Public Health England

165　(PHE) national laboratory testing surveillance system. The SIREN SQL database runs

166　automated data linkage with the laboratory surveillance system daily to extract new positive

167　and negative test results.

168

169   Participants are requested to complete online questionnaires at enrolment and fortnightly

170   intervals, capturing data on demographics, symptoms, testing and exposures (household,

171   community and occupational). Index of Multiple Deprivation a measure of neighbourhood

172   relative deprivation, calculated by the Office of National Statistics, was obtained through

173   linkage on participant postcode.

174

175   Data was extracted from all sources on 08 February 2021.

176

177   **Bias reduction**

178   Data were collected on potential confounders, including site and participant demographics to

179   enable adjusted analysis. Analysis was restricted to one manufacturer only, where sufficient

180   follow-up time had accrued; data was truncated on participants with an unreliable date of

181   second dose (<19 days). Sample date of a PCR positive result was used as the event date

182   which may have introduced some misclassification of vaccination status relative to infection

183   or onset in the period shortly after vaccination and informed our decision to calculate

184   cumulative vaccine effectiveness after suitable intervals (21 days post first dose and 7 days

185   post second dose), in order to focus on infections acquired since vaccination after a sufficient

186   interval for biological protection.

187

188   **Study size**

189   Prior to vaccine introduction calculations of the precision of effectiveness estimates were

190   performed on an estimated cohort size of 40,000, 65% seronegative at baseline, coverage

191   averaging at 75% in the follow-up period, and incidence in the follow-up period ranging from

192   0.5% to 5%. Precision estimates around effectiveness of 60% and 90% gave 95% confidence

193   intervals ranging from the widest for a VE of 60% (95%CI: 39-74) to the narrowest for a VE of

194   90% (95%CI: 88-92).

195

196   **Person time at risk**

197 Follow-up time for all participants started on 7 December 2020, the day before vaccine roll-

198 out began, with all participants contributing at least one day of follow-up unvaccinated.

199 Participants moved from unvaccinated to vaccinated within their assigned cohort on the date

200 of the first vaccination dose. Participants contributed person-time to follow-up until either an

201 event of interest (i.e. a new PCR positive in the negative cohort or a reinfection in the positive

202 cohort); the date of the suspect second dose for those with an unreliable date of second dose;

203 the date of their first dose for those vaccinated with the ChAdOx1 vaccine; or the censored

204 date.   We defined the end of follow-up in those who were not positive cases as the date of a

205 negative test or 05 February 2021 if the test was after this date, in order to avoid immortal time

206 bias. As symptomatic testing was done at any time of symptoms the most recent days could

207 be biased towards symptomatic testing, therefore, the end of follow-up was defined at a date

208 two days prior to the last date samples were available.

209

210 **Statistical methods**

211 Investigation of factors associated with vaccination was conducted using mixed effect

212 multivariable logistic regression model (with hospital site as a random effect) to investigate

213 confounding between demographic and occupational risk factors on the outcome variable

214 'ever vaccinated'. A backwards stepwise approach was used, removing variables from the

215 model sequentially with those with the least effect at univariable analysis removed first, and

216 goodness of fit was tested (likelihood ratio tests) after each change. Only the variables which

217 demonstrated strong evidence of association on vaccine coverage were retained in the final

218 model.

219

220 A mixed effect proportional hazards frailty model using a Poisson distribution was used to

221 calculate Hazard Ratios to compare time to infection in unvaccinated and vaccinated

222 participants to estimate the impact of the BNT162b2 vaccine on infection (including

223 asymptomatic and symptomatic as the primary outcome). As the main covariate of interest

224 (vaccination) changes as time elapses and the effect of vaccine changes over follow-up time,

225　we grouped time to infection into 12 vaccine intervals to analyse the short-term dynamics of

226　post vaccination protection in detail. The models were fitted by Poisson regression with a log

227　link, using COVID-19 infection as response, log of exposure times as an offset and dummies

228　for the time intervals as explanatory variables to allow for different piecewise constant

229　hazards.[12] The model fitting approach also provided estimates of the baseline hazard rates.

230　The hospital site was added into models as a random effect to account for the extra variation

231　and associated correlation that was not explained by risk/covariates variables. The frailty

232　model was also extended by including individual within the site as an addition random effect.

233　The results (not reported here) did not support heterogeneity among individuals after

234　controlling for site effect and therefore our final model does not include individual.   The fixed

235　covariates included in the model were age, ethnicity, comorbidities, region, job role, frequency

236　of COVID-19 patient contact, patient-facing role, workplace setting. Hazard ratios from 21 days

237　after first dose and seven days after second dose were calculated using a weighted average

238　method, the point at which an immunological response to the vaccine dose should have been

239　provoked. Vaccine effectiveness was calculated as 1 – adjusted Hazard Ratio (vaccinated

240　versus unvaccinated).

241

242　Three models were run on different cohorts within the study population. The main model

243　included the full study population and adjusted for cohort assignment. Models were then run

244　on the two cohorts separately, to provide estimates of vaccine effectiveness in the susceptible

245　population (negative cohort) and the positive cohort with natural immunity following prior

246　SARS-CoV-2 infection.

247

248　**Ethics**

249　The study was approved by the Berkshire Research Ethics Committee, Health Research

250　Authority (IRAS ID 284460, REC reference 20/SC/0230) on 22 May 2020; the vaccine

251　amendment was approved on 12/1/2021. The study is registered with ISRCTN (Trial ID:

252　ISRCTN11041050).

253 **Reporting**

254 The study follows the Strengthening the Reporting of Observational studies in Epidemiology

255 (STROBE) guidelines and the checklists are included in the Supplementary Appendix.[13]

256

257 **RESULTS**

258 **Characteristics of participants included in the analysis**

259 By 7 December 2020, 29,378 participants were enrolled and maintained in SIREN for the

260 England cohort; 23,324 met the inclusion criteria and were included in this analysis from 104

261 hospitals[1]. At the start date of follow-up (7 December 2020), 8,203 (35%) participants were

262 assigned to the positive cohort (antibody positive or had a previous antibody or PCR positive

263 test) and 15,121 (65%) were assigned to the negative cohort.

264

265 Most participants were female (84%; 19,692), of white ethnicity (89%; 20,424), in a patient-

266 facing role (86%; 20,054) and in a clinical discipline (66%; 15,502). A quarter (26%; n=5,874)

267 of participants had a reported medical condition; with asthma (n=2,893), obesity (n=1,988)

268 and diabetes (n=677) the most frequent.

269

270 The total follow-up time in this analysis was two calendar months and 1,106,905 participant

271 person-days, 710,587 person-days unvaccinated and 396,318 person-days vaccinated.

272 Participants were followed-up for a maximum of 59 days post first dose (median 21,

273 interquartile range: 13-31) and 39 days post second dose (median 23, interquartile range: 17-

274 28). Total person-days of follow-up in the negative cohort was 711,135 and 395,770 in the

275 positive cohort.

276

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[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).

305

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

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[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.

329   was no significant effect between days 4-9, with a significant protection from infection

330   increasing from day 10 onwards, and plateauing after 21 days. Following the second dose

331   a similar pattern is observed. The hazard ratios, adjusted and unadjusted for each time

332   period post vaccination in the full cohort and the negative cohort are provided in Appendix A

333   Tables 3a & 3b.

334

335   **DISCUSSION**

336   Our follow-up of this large cohort of over 23,000 HCWs, whose prior SARS-CoV-2 infection

337   history is known for two months after vaccine roll-out provides unique real-world data on the

338   short-term vaccine effectiveness of the BNT162b2 vaccine against both symptomatic and

339   asymptomatic infection. The regular PCR-testing of participants, regardless of symptom

340   status, allowed for the detection of asymptomatic infection, an important proxy for reduction in

341   transmission. Two months after roll-out commenced, 89% of our cohort had received at least

342   one dose of COVID-19 vaccine; 8% had received two doses. We detected modest variability

343   in coverage, with lower coverage observed in participants with prior infection, from Black,

344   Asian and minority ethnic backgrounds, and living in areas of higher deprivation.   We

345   estimated the vaccine effectiveness against infection for the BNT162b2 vaccine to be at least

346   70% 21 days after the first dose, increasing to at least 85% 7 days after the second dose in

347   our study population. This demonstrates that the BNT162b2 is effective against the B1.1.7

348   variant given its predominance throughout the studyperiod.[14]

349

350   The high vaccine coverage in SIREN may not be generalisable to UK HCWs or the general

351   population, as those who have self-selected to participate in a research study may not be

352   representative of UK HCWs or the population more generally.

353

354   With fewer of the cohort vaccinated with the ChAdOx1 vaccine, and the later roll-out resulting

355   in less follow-up time accrued, we are currently unable to investigate the effectiveness of the

356   ChAdOx1 vaccine within this study.

357

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.

366

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.

373

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,

385   not seen in our data. We also observed a significant trend of lower COVID-19 vaccination

386   coverage in those living in more deprived areas, corresponding to a population study of 23.4

387   million patients in the UK.[19]

388

389   Our analysis identified a reduced risk of infection in vaccinated individuals immediately (0-3

390   days) following the first dose, which cannot be plausibly explained by the immune response

391   to the vaccine; this is likely a deferral effect bias where those that are symptomatic, currently

392   PCR positive or have been recently exposed to a COVID-19 case may defer their

393   vaccination and be under-represented in accordance with national guidance.[20]

394

395   We found a vaccine effectiveness, at a given site, of at least 70% overall (72% in the negative

396   cohort) against both asymptomatic and symptomatic infection, from 21 days post-first dose of

397   the BNT162b2 vaccine. This is comparable to a single-centre Israeli HCW cohort study

398   vaccine effectiveness of 75% (95% CI 72 – 84), 15-28 days following first dose of BNT162b2

399   vaccine [16]. However, this study had no routine laboratory surveillance to pick up asymptomatic

400   cases and only detected cases if symptomatic, whereas SIREN had regular asymptomatic

401   testing; in addition, their adjustment for other potential risk factors was more limited.

402

403   Another population-level study in Israel reported a 51% reduction in PCR-confirmed SARS-

404   CoV-2 infections 13-24 days after individuals received the first dose of BNT162b2 vaccine,

405   compared to historical controls' 1-12 days [21]. This mirrors the 52.4% (95% CI: 29.5 - 68.4)

406   vaccine efficacy estimated by Pfizer-BioNTech researchers, between the first and second

407   dose.[6] Whilst follow up periods differed, the RCT included true controls and the Israeli study

408   included PCR-positivity regardless of symptom status compared to symptomatic confirmed

409   cases in the phase III BNT162b2 RCT. A preprint from researchers re-analysing the data from

410   the Israeli study using daily incidence of infection, calculated a vaccine effectiveness of 91%

411   at day 21 post-vaccination.[22] This estimate is closer to the 92.6% vaccine efficacy 14–21 days

412 after the first dose, calculated by researchers using data submitted by the manufacturers to

413 the Food and Drug Administration from vaccine trials.[23]

414

415 The differences in the vaccine effectiveness estimates may be due to the differences in

416 study design and populations included. Nonetheless, BNT162b2 is making a substantial

417 impact in reducing SARS-CoV-2 infection rates in vaccinated populations. A study with a

418 comparable methodology to SIREN, focussing on "Covid-19 Vaccine Effectiveness in

419 Healthcare Personnel in Clalit Health Services in Israel", is currently underway

420 [ClinicalTrials.gov number NCT04709003], but results are awaited. A notable difference is

421 that people in Israel that have recovered from SARS-CoV-2 infection are not eligible for

422 vaccination at present;[24] therefore, their population studies do not include the seropositive

423 people that would be present in a general population. Weekly swabbing of a sub-set of

424 asymptomatic and symptomatic participants was carried out in the Oxford-AstraZeneca RCT

425 and investigators reported reduced viral load and PCR positivity in the COVID-19 vaccinated

426 participants; a signal that transmission may be reduced by their vaccine.[25] This is the first

427 study that describes the reduction in all cases of infection with BNT162b2.

428

429 Most data on vaccinated UK individuals are from people aged >75years old, where vaccine

430 effectiveness may be lower due to immunosenesence.[27] The SIREN cohort is taken from

431 working age people, making the conclusions more relevant for the overall adult population.

432 However, the healthy worker effect bias may underestimate the disease impact compared to

433 the general population.[28]

434

435 Further work on this cohort is underway including measuring the impact of vaccination on

436 symptoms, serological responses, potential hospitalisations, and development of post-acute-

437 COVID. We will attempt to sequence infections occurring at least 21 days post vaccination to

438 determine proportion of novel variants.

439

440 This study clearly demonstrates that the vaccine does not prevent all cases of infection and

441 therefore HCWs will need to continue to wear personal protective equipment while caring for

442 all patients, observe physical distancing and other non-pharmaceutical measures in and

443 outside work and continue to perform regular asymptomatic testing (especially as typical

444 symptoms were reduced post vaccination) until COVID prevalence is considerably lower.

445

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461 **Trial Registration**

462 IRAS ID 284460, REC reference 20/SC/0230 Berkshire Research Ethics Committee, Health

463 Research Authority and Health and Care Research Wales approval granted 22 May 2020.

464 Trial registered with ISRCTN, Trial ID: ISRCTN11041050.

465 https://www.isrctn.com/ISRCTN11041050

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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 n (%)	Vaccinated n (%)	OR (95% CI)	p-value	aOR** (95% CI)	p-value
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

	Positive* n (%)	Negative n (%)	OR (95% CI)	p	Adjusted OR (95% CI)**	p
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

576 **Table 2: Effectiveness of the BNT162b2 COVID-19 vaccine against infection in SIREN**

577 **participants, stratified by cohort, between 7 December 2020 and 5 February 2021,**

578 **(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	-	-

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

583

584

FIGURES

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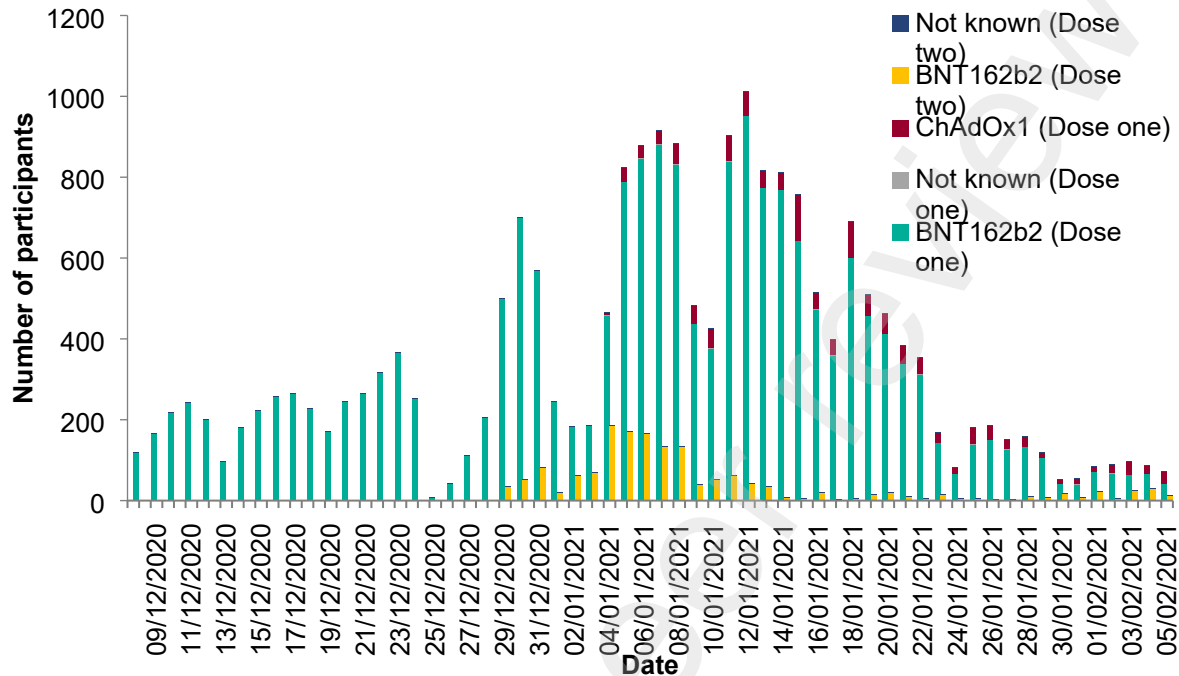

Figure 2a: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, full cohort (n=23,324)
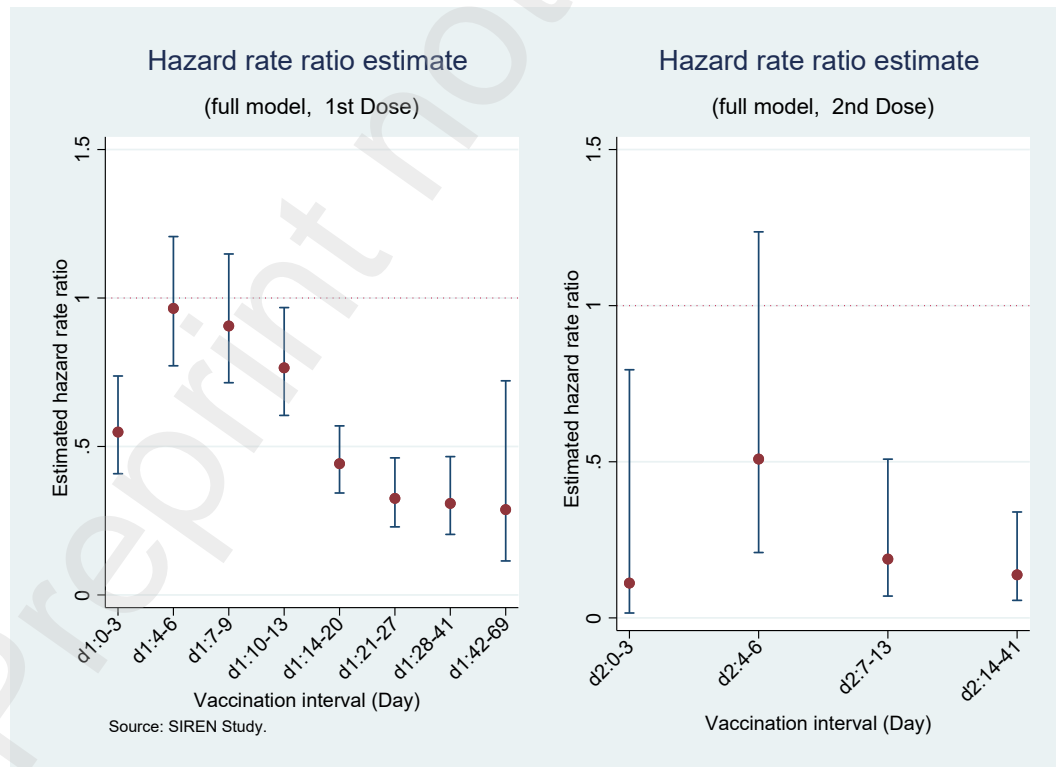
Figure 2b: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, negative cohort (n=15,121)

Hazard rate ratio estimate
(full model, negative cohort, 1st Dose)

Hazard rate ratio estimate
(full model, negative cohort, 2nd Dose)

Source: SIREN Study.