COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study

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1   **Protection against SARS-CoV-2 after COVID-19 vaccination and prior infection**

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ABSTRACT

Background

Understanding the duration and effectiveness of infection and vaccine-acquired SARS-CoV-2 immunity is essential to inform pandemic policy interventions, including the timing of vaccine-boosters. We investigated immunity duration and effectiveness in our prospective cohort of UK healthcare workers undergoing routine asymptomatic PCR testing.

Methods

Vaccine effectiveness (VE) was assessed (up to 10-months after first dose) and infection-acquired immunity by comparing time to PCR-confirmed infection in vaccinated and unvaccinated individuals using a Cox regression-model, adjusted by prior SARS-CoV-2 infection status, vaccine-manufacturer/dosing-interval, demographics and workplace exposures.

Results

Of 35,768 participants, 27% (n=9,488) had a prior SARS-CoV-2 infection. Vaccine coverage was high: 97% had two-doses (79% BNT162b2 long-interval, 8% BNT162b2 short-interval, 8% ChAdOx1). Between 07/12/2020 and 21/09/2021, 2,747 primary infections and 210 reinfections were noted. Among participants without previous infection, adjusted VE (aVE) decreased from 85% (95%CI 72%-92%) 14-73 days after dose-2 to 51% (95%CI 22%-69%) >6-months; with no significant difference for short-interval BNT162b2 but significantly lower aVE (50% (95%CI 228%-77%) 14-73 days after dose-2 from ChAdOx1. Infection-acquired immunity showed evidence of waning after a year without vaccination, but remained consistently over 90% in those subsequently vaccinated, even in those infected over 18-months ago.

Conclusion

60   Two doses of BNT162b2 vaccination is associated with high short-term protection to SARS-

61   CoV-2 infection, which wanes significantly after six months. Infection-acquired immunity

62   boosted with vaccination remains high over a year after infection.

63   Trial registration number

64   ISRCTN11041050

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BACKGROUND

Understanding the durability of the immune response to SARS-CoV-2 infection and COVID-19 vaccination remains critical to the global COVID-19 response. Twenty months after emergence, SARS-CoV-2 has caused millions of deaths,[1] and widespread disruption to global health and economies. The development and mass deployment of COVID-19 vaccines within a year was unprecedented. COVID-19 vaccines have demonstrated short-term effectiveness in real-world studies, reducing both symptomatic and asymptomatic infection, severity and secondary transmission.[2-5] The duration of this protection over longer periods remains uncertain and requires ongoing study.

Population uptake of COVID-19 vaccination in the UK (aged over 12 years) is 80.4% for two doses,[6] and prioritized groups (health and social care workers and the clinically vulnerable), are now over six months after their second dose. Following concerns about potential immunity waning at this point,[7-11] and in the context of sustained high levels of community infections,[6] the UK Government initiated a roll-out of booster vaccination to priority groups in September 2021.[12] Improved understanding and characterization of vaccine effectiveness at longer intervals and potential variation by demographic factors, vaccine schedules and history of SARS-CoV-2 infection is urgently required to optimize vaccination strategy.

The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study, a large cohort of healthcare workers undergoing fortnightly asymptomatic PCR testing, had over 30% of participants testing seropositive at enrolment.[5,13,14] In this analysis we aim to determine the level and durability of protection against SARS-CoV-2 infection in the SIREN cohort from March 2020 to September 2021 by estimating: vaccine effectiveness following two doses of COVID-19 vaccine, considering manufacturer and dosing interval, in participants without prior infection; and protection from reinfection conferred by prior infection plus COVID-19 vaccine.

METHODS

Study design and participants

The SIREN study is a multicenter prospective cohort study of healthcare workers aged 18 years and older across the UK.

Data sources and measurement

Participants undergo fortnightly SARS-CoV-2 PCR testing (supplemented by widespread lateral flow testing), monthly antibody testing and complete regular questionnaires (including symptom data). This data collection is described elsewhere.[5]

Vaccination data (manufacturer, dates) were obtained via linkage on personal identifiers from national COVID-19 vaccination registries in each health administration and directly from participants in their fortnightly questionnaires. Dosing interval was categorized as 'short' if dose-two was administered up to 6-weeks post dose-one and 'long' if ≥6-weeks.[15]

Serum samples from all participant baseline visits are collected centrally and tested at the United Kingdom Health Security Agency (UKHSA) central testing laboratory at Porton Down using the semi-quantitative Elecsys Anti-SARS-CoV-2 nucleocapsid (N) protein assay and fully quantitative Elecsys Anti-SARS-CoV-2 spike (S) protein assay (Roche Diagnostics).

Explanatory variables and exclusion criteria

Participants were assigned to one of two cohorts at the start of analysis time: participants in the naïve cohort had no history of SARS-CoV-2 positivity and the positive cohort were those who had ever received a PCR or antibody positive result consistent with prior SARS-CoV-2 infection.

Participants were excluded from this analysis if event or cohort assignment could not be accurately completed. This included participants: without PCR tests during follow-up, with previous infection occurring on or after vaccination date, without an onset date for primary infection (PCR positive or COVID-19symptom onset).

Outcomes

The primary outcome was a PCR-confirmed SARS-CoV-2 infection, irrespective of symptom status, that met the definition of a primary infection in the naïve cohort or a reinfection in the positive cohort (two PCR positives samples ≥90 days apart or a new PCR positive sample ≥28 days after an antibody positive result consistent with previous infection).

Person time at risk

Follow-up began on 07 December 2020, the day before COVID-19 vaccination was introduced to the UK, and continued until 21 September 2021, covering 10 calendar months. All participants enrolled on or before 07 December 2020 contributed follow-up time from 07 December 2020 onwards. Participants enrolled after 07 December 2020 began contributing follow-up time from their enrolment date (delayed entry). Participants who had a primary infection (before vaccination) during follow-up were moved into the positive cohort 90 days after their PCR positive date, at which point they were considered at risk of reinfection. End of follow-up time for individual participants was either date of primary infection (negative cohort), date of reinfection (positive cohort) or last PCR negative test.

Statistical methods

We used a Cox proportional hazards model with delayed entry, the outcome being time-to-infection with a positive PCR test, stratified by age group, region, workplace setting and frequency of exposures to COVID-19 patients We chose to stratify over levels of the above categorical predictors as they were significant when controlled for, but did not satisfy the Proportional Hazards assumption (Schoenfield test, per predictor and global). We also controlled for sex and ethnicity, as we noticed that these predictors are significant, lead to an increase in the likelihood value and Wald Statistic and satisfy the proportional hazard assumptions (Schoenfeld test).

 The model accounted for calendar time, given the varying infection rate, via the baseline hazard, that could take any functional form. In this model, the hazard is assumed as:

143 $$h_i(t) = h_{0i}(t) exp\left(\beta_1 x_1 + \cdots + \beta_k x_k\right),$$

144 with a time-varying baseline hazard $h_{0i}(t)$ for each stratum. We estimated the parameters

145 β, equivalently hazard ratios HR= exp(β), and report vaccine effectiveness and protection

146 from primary infection calculated as 1-HR, together with Wald's confidence intervals. The

147 estimates of the HRs are independent from the baseline hazard, on which no assumption is

148 made.

149 Analysis time began on 07 December 2020, shortly before the second wave peaked,

150 continuing through Spring 2021 and into the third wave (Supplementary Figure iii); thus,

151 accounting for a varying hazard rate was crucial.

152 The main predictors – vaccine status and previous infection status - were categorical and

153 time-varying. We grouped on the time to vaccination and divided follow-up time into

154 unvaccinated and post-vaccination time intervals. We also grouped previous infection status

155 into three categories: before primary infection (naïve), ≤12 and >12 months after primary

156 infection. We used robust variance estimates to guard against the potential for unmeasured

157 confounders at hospital organization (site) level.

158

159 We fitted the model first on the naïve cohort, estimating vaccine effectiveness over time

160 (Table 2). Here, post vaccination intervals were categorized by manufacturer and dosing

161 interval, the latter to explore differences in protection in those receiving dose two closer in

162 time to their first dose. We then focussed on all BNT162b2 recipients, including those

163 infected before vaccination, and fitted a model with interaction of time since primary infection

164 and time since vaccination. ChAdOX1 recipients and the categorization by dosing interval for

165 BNT162b2 were dropped because of small numbers in the positive cohort. This allowed us

166 to investigate vaccine effectiveness in previously infected individuals. We report these

167 estimates in Table 3. In Tables 2 and 3 we also report estimates from an unadjusted model,

168 without stratifying or controlling for any predictor other than time since vaccination and

169   infection. Goodness of fit was assessed via likelihood ratio test (against the null model) and

170   Akaike Information Criterion (AIC) values. The widths of the confidence intervals have not

171   been adjusted for multiplicity and cannot be used to infer effects.

172   We performed sensitivity analyses to assess the extent of depletion-of-susceptible bias and

173   the impact of excluding positive-cohort participants without a reliable date of primary

174   infection. All sensitivity analyses gave similar results with those presented here, but more

175   uncertain estimates (see Supplementary Appendix). We used STATA software (version

176   15.1; StataCorp LLC, College Station, TX, USA) for all analyses. Results were independently

177   replicated in R (v. 4.1.1, survival package v.3.2-13). Our annotated code is available

178   (https://github.com/SIREN-study/SARS-CoV-2-Immunity).

179   This study was registered, number ISRCTN11041050, and received approval from the

180   Berkshire Research Ethics Committee on 22 May 2020. Reporting of the study follows the

181   Strengthening the Reporting of Observational studies in Epidemiology guidelines.[16]

182

183   **RESULTS**

184   **Study population**

185   The SIREN study enrolled 44,546 participants between 18 June 2020 and 23 April 2021

186   from 135 sites across the UK; n=35,768 met the inclusion criteria for this analysis

187   (Supplementary Figure 1). Participants are described in Table 1, and were predominantly

188   female (84%), with a median age of 46 years (IQR 36-54), see Supplementary Table 2 for

189   comparison with national population. We assigned 26,280 participants to the naïve cohort

190   and 9,488 to the positive cohort at analysis start time. The positive cohort were more likely

191   to be male, younger, from Black, Asian and ethnic minority backgrounds, work in clinical

192   roles and report more frequent exposure to COVID-19 patients (Table 1). By the end of

193   analysis time, 97% of the cohort had received two vaccine doses: 78.5% BNT162b2 long-

194   interval, 8.6% BNT162b2 short-interval and 7.8% ChAdOX1 (Table 1, Supplementary Figure

195 3). We identified no major demographic differences between participants by vaccine

196 schedule (Supplementary Table 3).

197 Follow-up time varied by participant, with a total of 7,482,388 participant person-days, of

198 which 998,270 person-days were unvaccinated, and 6,430,118 person-days vaccinated

199 (from date of first dose). 62,291 PCR tests were performed in the unvaccinated follow-up

200 period and 427,951 PCR tests in the vaccinated follow-up period, with an average test

201 interval of 16 days per test in the unvaccinated period and 15 days per test in the vaccinated

202 period. In the naïve cohort, 358,346 tests (14.8 days per test) were done and 131,896 tests

203 were done in the previously infected cohort (14.3 days per test).

204

205 **Outcome**

206 Primary infections were noted in 2,747 participants during follow-up and reinfections were

207 seen in 210, with cases peaking at the end of December 2020 and declining by March-April

208 2021, before increasing in May 2021, which mirrored national trends (Supplementary Figure

209 3). Looking at symptom status 14-days before or after the PCR positive date, among primary

210 infections 1,673 (61%) reported COVID-19-related symptoms, 368 (13%) reported other

211 symptoms, 118 (4%) reported no symptoms and 588 (21%) did not provide symptom data.

212 In contrast among the reinfections, 71 (34%) reported COVID-19-related symptoms, 42

213 (20%) reported other symptoms, 45 (21%) reported no symptoms and 52 (25%) did not

214 provide symptom data. Considering self-reported hospital attendance, 357 (13%)

215 participants with primary infections reported hospital attendance for COVID-19-related

216 symptoms compared to 18 (8%) reinfections.

217

218 **Vaccine effectiveness against primary infection**

219 Among participants without previous SARS-CoV-2 infection, two doses of BNT162b2

220 vaccine at long interval was associated with an 85% lower risk of infection (95% CI 72%-

221 92%) i.e. an adjusted vaccine effectiveness (aVE), in the first two months after the

222 development of the full immune response (14-73 days after second dose) (Table 2, Figure 1,

223 Supplementary Table 4).

224 Over time, aVE declined but remained high at 68% (95% CI 54%-77%) 4-6 months after

225 dose-two. After six months we saw evidence of waning, with aVE of 51% (95% CI 22%-

226 69%).

227 A similar trend was observed for BNT162b2 dose two short-interval group, with higher

228 protection at 14-73 days (aVE 89% (95% CI 78%-94%) decreasing to 53% (95% CI 28%-

229 69%) after 6 months. We found no significant difference in protection after dose-two between

230 BNT162b2 long and short inter-vaccination intervals, with HR for infection of 1.34 (95% CI

231 0.58-3.10) at 14-73 days using short interval as the reference group.

232 For ChAdOX1, aVE from two doses was 58% (95% CI 23%-77%) 14-73 days after second

233 dose. Effectiveness did not differ significantly with longer intervals after dose-two, with

234 overlapping confidence intervals of VE reflecting the small number of participants

235 contributing to this estimate (Table 2, Figure 1). Compared to ChAdOX1, we found that

236 Pfizer short was 74% more effective (95% CI 36%-89%) and Pfizer long was 65% more

237 effective (95% CI 21%-85%), in the interval 14-73 days.

238 The model's Wald Chi-Square was 371.46 (31 degrees of freedom), with AIC=15367.

239 **Durability of protection without infection following primary infection**

240 Among 6169 participants contributing follow-up time unvaccinated and up to a year after

241 primary infection, who were predominately infected in Spring 2020 and followed-up in the pre

242 Delta-period, their risk of reinfection was 86% (95% 81%-89%) lower than the risk of primary

243 infection in the unvaccinated infection-naïve cohort (Table 2, Figure 3, Supplementary table

244 4). Protection showed evidence of significant waning over a year after infection, reducing to

245   69% (95% CI 38%-84%), with protection in the first year being 54% higher (95% CI 3%-78%)

246   than after more than a year.

247   **Durability of protection with infection and vaccination combined**

248   In contrast, looking at the impact of vaccination on the cohort with prior COVID-19 infection

249   (positive cohort), using naïve unvaccinated volunteers as the reference group (Table 3,

250   Figure 2), a beneficial boosting of infection-acquired immunity was apparent, with combined

251   protection generally over 90% following vaccination (both dose 1 and dose 2). Protection

252   waning was not found either over a year after infection or over six-months following

253   vaccination.   The model's Wald Chi-Square was 789.68 (30 degrees of freedom), with

254   AIC=14841.

255

256   **DISCUSSION**

257   Eighteen months after the emergence of SARS-CoV-2 and ten months after the rapid

258   deployment of COVID-19 vaccines, we have assessed the durability of protection from

259   SARS-CoV-2 infection conferred by both infection-acquired and vaccine-acquired immunity.

260   Our cohort of 26,280 healthcare workers without prior infection primarily received two doses

261   of BNT162b2 administered at a long inter-vaccine interval, which was associated with

262   considerably reduced risk of infection over the first 6 months, peaking between 72% and

263   92% in the first two months; however, we found evidence of significant waning immunity,

264   with protection declining to between 22% and 69% after six months. We found no difference

265   in risk of infection following two doses when comparing BNT162b2 short interval with

266   BNT162b2 long interval, although we found significantly lower protection from two doses of

267   ChAdOX1 compared to BNT12b2. Of note, the period of waning coincided with the Delta

268   variant being the predominant circulating strain, which may account for the more pronounced

269   waning of protection in our cohort, given the reported reduced vaccine effectiveness against

270   Delta.[17]

271 Unvaccinated participants with prior infection had between 81% and 89% reduced risk of

272 infection compared to unvaccinated naïve participants at up to a year after infection, but we

273 found evidence of protection waning over a year after infection. Delivery of vaccination to

274 individuals after prior infection appears to boost and extend their immunity, and we found no

275 indication of waning even well over a year after primary infection. Protection in our cohort of

276 participants vaccinated after previous infection was similar to levels reported for a three-

277 course vaccination against symptomatic infection.[18]

278 Our finding of reduced protection from infection following two doses of vaccination after six

279 months strengthens the accruing evidence base. Our design overcomes several biases of

280 recent studies, including underestimation of the proportion of participants with prior

281 infection.[19] Previous studies have typically investigated symptomatic infection and utilized

282 test-negative case-control or retrospective cohort designs using national testing surveillance

283 data.[7,9,11] We note that these real-world studies have found consistently lower protection and

284 more pronounced waning than the recent BNT162b2 clinical trial, which reported vaccine

285 efficacy against symptomatic infection of 83.7% (95% CI, 74.7 to 89.9) 4-6 months after

286 dose-2,[20] likely related to the reduced vaccine effectiveness reported against the Delta

287 variant.[17] The significantly lower protection observed in this study after ChAdOX1 compared

288 to BNT162b2 has also been found in other recent studies.[7,20] Several studies have observed

289 lower antibody titers following ChAdOx1 vaccination than BNT162b2,[21,22] and a shorter

290 interval to fall below a putative protective antibody threshold from this lower baseline has

291 been proposed as a causal mechanism for the lower vaccine effectiveness.[20] We found no

292 difference in protection against infection after two doses of BNT162b2 between short and

293 long-interval despite evidence of significantly higher antibody, B-cell and T-cell responses in

294 recipients of long-interval compared to short-interval vaccination regimens,[15,23,24] and higher

295 VE against symptomatic infection from one observational study.[15] Plausibly the threshold to

296 prevent all infections may be lower than that for symptomatic infection.

297 Studies to date have shown more durable protection against severe outcomes of

298 hospitalization and death following vaccination.[7,25] Whilst we have estimated VE against all

299 infections, including asymptomatic infections that have limited clinical impact, a reduction in

300 VE against infection will increase transmission and risk of infection to high-risk individuals,

301 some of whom will progress to severe disease. Given the profile of our cohort, being

302 relatively young and healthy, and the rarity of severe disease in this study, we are unable to

303 assess protection against severe outcomes.

304 It remains unclear how long immune protection will last after previous infection due to the

305 limited length of follow-up period; however, modelling has suggested that protection could

306 last for up to 61 months, and other studies have reported protection ranging from 5-12

307 months.[21,26][27-29] In our cohort, we have demonstrated that protection from primary infection

308 remains high at up to a year but then begins to wane. It is important to highlight that most

309 unvaccinated follow-up post-infection occurred in the pre-Delta wave, with most of this

310 cohort infected in Spring 2020 and vaccinated by end of January 2021.   Our ability to study

311 infection-acquired immunity in unvaccinated individuals at longer intervals is now limited

312 given the very small number of participants in our cohort remaining unvaccinated. It is

313 possible that the sustained infection-acquired protection in our cohort is affected by repeated

314 low dose occupational exposure to COVID-19,[30] and therefore, less generalizable to

315 populations at lower exposure. It is also possible that sustained protection results from a

316 broader diversity of T-cell immunity against different SARS-CoV-2 spike protein epitopes

317 emerging following infection, enhancing protection against variants and inducing long-lasting

318 memory T-cell populations.[27,31,32] Although our finding of greater protection associated with

319 infection-acquired immunity has been demonstrated by other authors,[33,34] others have

320 reported vaccine-acquired immunity to be equivalent,[35,36] or superior.[37] Whilst infection-

321 acquired immunity is associated with high protection, in the absence of vaccination it wanes

322 after a year. We have demonstrated additional benefit from vaccination in previously

323 infected participants, in line with previous studies,[34,38,39] and our finding of high levels of

324   protection associated with immunity from infection plus vaccination has also been observed

325   previously.[40] Until thresholds for protective antibody titers against SARS-CoV-2 infection are

326   established, it is challenging to accurately estimate how much vaccine-induced immunity is

327   required to prevent reinfection at an individual level.

328   Key strengths of our study are the size of the cohort undergoing frequent testing

329   independent of disease status, with an average PCR test interval of 16.6 days in

330   unvaccinated time and 14.5 days per test in vaccinated follow-up time, supplemented by the

331   widespread use of lateral flow testing, which means we can be confident that most infections

332   were detected. As a well-defined cohort, we can simultaneously investigate vaccination and

333   prior infection status and adjust for important confounders, including workplace exposures.

334   The most important limitation of our study is the relatively small number of participants

335   continuing to contribute follow-up time to key vaccination exposures: unvaccinated,

336   ChAdOx1 and BNT162b2 short interval. This particularly affects the precision of estimates

337   and our ability to assess potential waning following two-doses of ChAdOx1. We consider

338   that the strengths of our study design and speed of vaccine deployment significantly limit the

339   impact of depletion-of-susceptible bias (which particularly affects studies on vaccine-

340   waning),[19] and demonstrated the lack of impact of this bias in our sensitivity analysis

341   (Supplementary Appendix); however, we recognize some residual confounding may remain.

342   **Conclusion**

343   Two doses of BNT162b2 vaccination given with a short or long-interval were associated with

344   considerably reduced risk of SARS-CoV-2 infection (asymptomatic and symptomatic) in the

345   short-term, but this protection wanes after six months, during a period where Delta

346   predominates. Protection associated with two doses of ChAdOX1 is considerably lower

347   overall. The highest and most durable protection is observed in those who received one or

348   two doses of vaccine after a primary infection. Strategic use of booster vaccine doses to

349   avert waning of protection (particularly in double vaccinated previously uninfected

350   individuals) may reduce infection and transmission in the ongoing response to COVID-19.

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Tables and Figures

Table 1: Description of participant demographics, by cohort assignment, June 2020 to
September 2021

Demographics	Total n (%)	Naïve cohort n (%)	Positive cohort n (%)
Gender			
Male	5699 (15.9)	4051 (15.4)	1648 (17.4)
Female	30017 (83.9)	22190 (84.4)	7827 (82.5)
Other	52 (0.1)	39 (0.1)	13 (0.1)
Age group			
Under 25	1297 (3.6)	935 (3.6)	362 (3.8)
25 to 34	7106 (19.9)	5023 (19.1)	2083 (22.0)
35 to 44	8848 (24.7)	6580 (25.0)	2268 (23.9)
45 to 54	10874 (30.4)	8007 (30.5)	2867 (30.2)
55 to 64	7085 (19.8)	5283 (20.1)	1802 (19.0)
Over 65	558 (1.6)	452 (1.7)	106 (1.1)
Ethnicity			
White	31634 (88.4)	23610 (89.8)	8024 (84.6)
Asian	2486 (7.0)	1581 (6.0)	905 (9.5)
Black	621 (1.7)	381 (1.4)	240 (2.5)
Mixed race	535 (1.5)	380 (1.4)	155 (1.6)
Other ethnic group	427 (1.2)	278 (1.1)	149 (1.6)
Prefer not to say	65 (0.2)	50 (0.2)	15 (0.2)
Medical conditions category			
No medical condition	26670 (74.6)	19569 (74.5)	7101 (74.8)
Immunosuppression	803 (2.2)	623 (2.4)	180 (1.9)
Chronic respiratory conditions	4439 (12.4)	3306 (12.6)	1133 (11.9)
Chronic non-respiratory conditions	3856 (10.8)	2782 (10.6)	1074 (11.3)
Staff group			
Administrative/Executive (office based)	5434 (15.2)	4280 (16.3)	1154 (12.2)
Nursing	12184 (34.1)	8658 (32.9)	3526 (37.2)
Healthcare Assistant	2901 (8.1)	1994 (7.6)	907 (9.6)
Doctor	4248 (11.9)	3053 (11.6)	1195 (12.6)
Midwife	777 (2.2)	582 (2.2)	195 (2.1)
Physiotherapist/Occupational Therapist/SALT	1438 (4.0)	996 (3.8)	442 (4.7)
Estates/Porters/Security	530 (1.5)	389 (1.5)	141 (1.5)
Pharmacist	737 (2.1)	582 (2.2)	155 (1.6)
Healthcare Scientist	1390 (3.9)	1147 (4.4)	243 (2.6)
Student (Medical/Nursing/Midwifery/Other)	1200 (3.4)	867 (3.3)	333 (3.5)
Other	4929 (13.8)	3732 (14.2)	1197 (12.6)
Occupational setting			
Office based	7002 (19.6)	5481 (20.9)	1521 (16.0)
Patient facing (non-clinical)	1378 (3.9)	1064 (4.0)	314 (3.3)
Outpatient	7341 (20.5)	5662 (21.5)	1679 (17.7)

Maternity/Labour Ward	477 (1.3)	361 (1.4)	116 (1.2)
Ambulance/Emergency Department/Inpatient Wards	6456 (18.0)	4225 (16.1)	2231 (23.5)
Intensive Care	1669 (4.7)	1273 (4.8)	396 (4.2)
Theatres	866 (2.4)	657 (2.5)	209 (2.2)
Other	10579 (29.6)	7557 (28.8)	3022 (31.9)
Patient contact			
No	5105 (14.3)	4053 (15.4)	1052 (11.1)
Yes	30663 (85.7)	22227 (84.6)	8436 (88.9)
Frequency of COVID-19 patient contact			
Never	12752 (35.7)	10290 (39.2)	2462 (25.9)
Every day	8797 (24.6)	5585 (21.3)	3212 (33.9)
Once week	6229 (17.4)	4340 (16.5)	1889 (19.9)
Once month	3257 (9.1)	2368 (9.0)	889 (9.4)
Less month	4733 (13.2)	3697 (14.1)	1036 (10.9)
Index of Multiple Deprivation			
5 (least deprived)	8871 (24.8)	6563 (25.0)	2308 (24.3)
4	8073 (22.6)	5982 (22.8)	2091 (22.0)
3	7515 (21.0)	5537 (21.1)	1978 (20.8)
2	6020 (16.8)	4408 (16.8)	1612 (17.0)
1 (most deprived)	3858 (10.8)	2680 (10.2)	1178 (12.4)
Not known	1431 (4.0)	1110 (4.2)	321 (3.4)
Geographical area			
East Midlands	2825 (7.9)	1963 (7.5)	862 (9.1)
East of England	3363 (9.4)	2415 (9.2)	948 (10.0)
London	3688 (10.3)	2432 (9.3)	1256 (13.2)
North East	647 (1.8)	453 (1.7)	194 (2.0)
North West	3429 (9.6)	2174 (8.3)	1255 (13.2)
South East	3548 (9.9)	2568 (9.8)	980 (10.3)
South West	5540 (15.5)	4503 (17.1)	1037 (10.9)
West Midlands	2717 (7.6)	1900 (7.2)	817 (8.6)
Yorkshire and Humber	2644 (7.4)	1765 (6.7)	879 (9.3)
Scotland	5449 (15.2)	4646 (17.7)	803 (8.5)
Northern Ireland	1127 (3.2)	888 (3.4)	239 (2.5)
Wales	791 (2.2)	573 (2.2)	218 (2.3)
Vaccination status by 21 Sep 2021			
2-doses BNT162b2 Long interval	28078 (78.5)	21427 (79.2)	6651 (76.4)
2-doses BNT162b2 Short interval	3059 (8.6)	2493 (9.2)	566 (6.5)
2-doses ChAdOX1	2803 (7.8)	2002 (7.4)	801 (9.2)
1-dose (any)	937 (2.6)	652 (2.4)	285 (3.3)
Unvaccinated	891 (2.5)	483 (1.8)	408 (4.7)
Total	**35,768**	**26,280 (73.5)**	**9,488 (26.5)**

493 Positive cohort assignment: 83% seropositive (72% on UKHSA testing), 17% seronegative with historic antibody/PCR positive).
494 Primary infections in the positive cohort occurred in March-May 2020 for 2,576 (57.6%) participants, June-August for 167
495 (3.7%) and September-December for 1,728 (38.6%). * Index of Multiple Deprivation (IMD), which is a measure of
496 neighbourhood relative deprivation calculated by the Office of National Statistics, was obtained through linkage with participant
497 postcodes

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Table 2: Incidence of SARS-CoV-2 infections and effectiveness of COVID-19 vaccines against infection by dose, manufacturer and dosing interval, among SIREN participants without prior SARS-CoV-2 infection (naïve cohort) 07 December 2020 to 21 September 2021

Vaccine status	Number of participants	Number of days of follow up	All primary infections (symptomatic & asymptomatic)			
			Number of primary infections	Crude Incident rate (per 10,000)	VE (1-HR) 95% CI	aVE (1-HR) 95% CI
Unvaccinated	18094	649643	1038	15.98	Reference	Reference
Vaccinated 1 dose Time since vaccine *BNT162b2*						
21 – 27 days	15549	102894	52	5.05	0.59 (0.44-0.71)	0.59 (0.42-0.71)
28 – 41 days	15247	201531	60	2.98	0.64 (0.47-0.76)	0.66 (0.52-0.76)
42 – 55 days	15691	207857	29	1.4	0.71 (0.56-0.81)	0.70 (0.54-0.81)
> 55 days	16376	341183	53	1.55	0.67 (0.53-0.77)	0.63 (0.46-0.75)
ChAdOX1						
21 – 27 days	1471	10204	2	1.96	0.63 (-0.61-0.92)	0.63 (-0.80-0.92)
28 – 41 days	1495	20496	1	0.49	0.87 (0.13-0.98)	0.85 (0.16-0.97)
42 – 55 days	1494	20445	3	1.47	0.42 (-0.66-0.80)	0.32 (-0.87-0.75)
> 55 days	1470	38308	10	2.61	0.24 (-0.56-0.63)	0.09 (-0.87-0.55)
Vaccinated 2 doses Time since vaccine *BNT162b2 long-interval*						
14 – 73 days	18562	1063102	16	0.15	0.85 (0.71-0.93)	0.85 (0.72-0.92)
74 – 133 days	17332	950734	264	2.78	0.70 (0.60-0.78)	0.66 (0.53-0.75)
134 – 193 days	13539	528245	479	9.07	0.73 (0.64-0.79)	0.68 (0.54-0.77)
>193 days	2261	20774	81	38.99	0.46 (0.19-0.64)	0.51 (0.22-0.69)
BNT162b2 short-interval						
14 – 73 days	2259	118505	10	0.84	0.85 (0.70-0.92)	0.89 (0.78-0.94)
74 – 133 days	2238	130389	6	0.46	0.62 (0.19-0.82)	0.58 (0.18-0.79)
134 – 193 days	2122	118192	47	3.98	0.58 (0.39-0.70)	0.50 (0.26-0.67)
>193 days	1706	69352	87	12.54	0.62 (0.45-0.74)	0.53 (0.28-0.69)
ChAdOX1						
14 – 73 days	1414	79806	15	1.88	0.52 (0.15-0.73)	0.58 (0.23-0.77)
74 – 133 days	1213	59593	51	8.56	0.54 (0.32-0.68)	0.50 (0.29-0.65)
> 133 days	715	16936	26	15.35	0.67 (0.40-0.82)	0.72 (0.39-0.87)

Crude incident rate: number of infections/days of follow-up (*10,000), does not adjust for variable baseline hazard. VE: unadjusted Vaccine Effectiveness, model adjusted for time since vaccination (combined with dosing interval and manufacturer) and baseline hazard only. aVE: adjusted Vaccine Effectiveness, model adjusted for baseline hazard time since vaccination (combined with dosing interval and manufacturer) and constant predictors gender and ethnicity, and stratified over workplace setting, frequency of contact with COVID-19 patients, geographical area (of workplace), age. More details are available in supplementary Table iii.

Table 3: Incidence of SARS-CoV-2 reinfections and effectiveness of the BNT162b2 mRNA COVID-19 vaccine against reinfection among SIREN participants with prior SARS-CoV-2 infection, 07 December 2020 to 21 September 2021

| Vaccine status	Number of participants	Number of days of follow up	All reinfections (symptomatic & asymptomatic)			
			Number of reinfections	Crude Incident rate (per 10,000)	VE (1-HR) 95% CI	aVE (1-HR) 95% CI
Primary infection ≤1 year						
Unvaccinated	6169	258088	58	2.25	0.82 (0.76-0.87)	0.86 (0.81-0.89)
Vaccinated dose 1 21+ days	7381	303281	13	0.43	0.91 (0.84-0.95)	0.92 (0.86-0.95)
Vaccinated dose 2						
14 – 73 days	5075	201580	8	0.40	0.81 (0.60-0.91)	0.84 (0.67-0.92)
74 – 133 days	2480	119013	12	1.01	0.90 (0.82-0.95)	0.92 (0.83-0.96)
134 – 193 days	1533	51893	13	2.51	0.91 (0.85-0.95)	0.92 (0.85-0.95)
>193 days	192	3346	3	8.97	0.75 (-0.19-0.95)	0.86 (0.27-0.97)
Primary infection >1 year						
Unvaccinated	486	50041	12	2.40	0.71 (0.42-0.85)	0.69 (0.38-0.84)
Vaccinated dose 1 21+ days	1642	38422	2	0.52	0.90 (0.60-0.97)	0.94 (0.62-0.99)
Vaccinated dose 2						
14 – 73 days	4852	234484	2	0.09	0.93 (0.72-0.98)	0.94 (0.75-0.99)
74 – 133 days	4970	261549	9	0.34	0.96 (0.92-0.98)	0.97 (0.93-0.98)
134 – 193 days	3772	137473	18	1.31	0.95 (0.91-0.97)	0.93 (0.89-0.96)
>193 days	654	15808	2	1.27	0.96 (0.84-0.99)	0.95 (0.82-0.99)

Crude incident rate: number of infections/days of follow-up (*10,000), does not adjust for variable baseline hazard. In order to provide absolute protection, the reference group is the naïve unvaccinated group, refer to Table 2 for details on this group. For the unvaccinated group, VE refers to protection against reinfection, comparing infection rates in the unvaccinated cohort with prior infection with the unvaccinated cohort without prior infection. Unadjusted absolute protection against reinfection: model adjusted for combinations of time since vaccination with BNT162b2 and primary infection, and baseline hazard only. Adjusted absolute protection against reinfection: model adjusted for baseline hazard, combinations of time since vaccination with BNT162b2 and primary infection and constant predictors gender and ethnicity, and stratified over workplace setting, frequency of contact with COVID-19 patients, geographical area (of workplace), age. More details are available in supplementary Table iv

Figure 1: Adjusted Vaccine Effectiveness over time after two doses: BNT162b2 (Pfizer-BioNTech) short and long interval and ChAdOX1 (combined short and long interval), among SIREN participants without prior SARS-CoV-2 infection (naïve cohort) 07 December 2020 to 21 September 2021
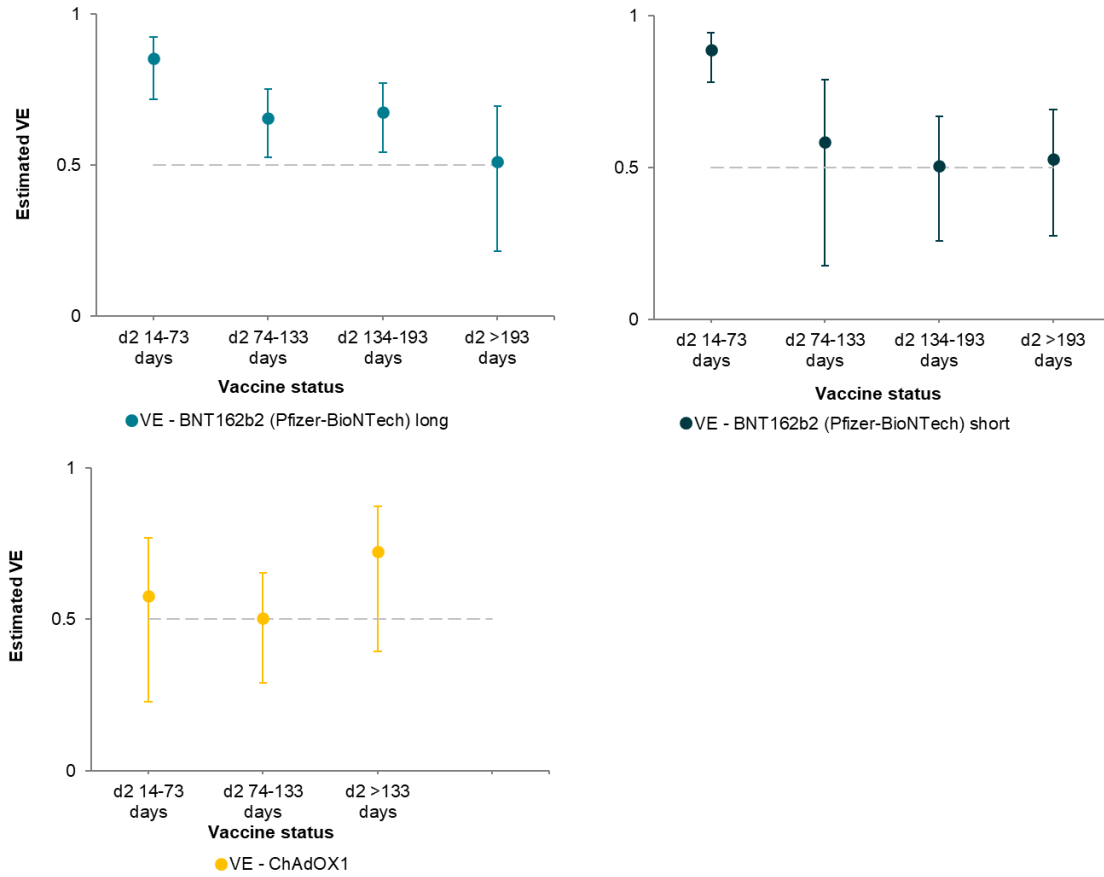
Figure 2: Protection following reinfection under different COVID-19 vaccination scenarios, up to 18 months following infection, among SIREN participants with prior SARS-CoV-2 infection, 07 December 2020 to 21 September 2021