

1 **Do antibody positive healthcare workers have lower SARS-CoV-2**
2 **infection rates than antibody negative healthcare workers? Large**
3 **multi-centre prospective cohort study (the SIREN study), England:**
4 **June to November 2020**
5

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24 **ABSTRACT**

25 Background: There is an urgent need to better understand whether individuals who have
26 recovered from COVID-19 are protected from future SARS-CoV-2 infection.

27 Methods: A large multi-centre prospective cohort was recruited from publicly funded hospital
28 staff in the UK. Participants attended regular SARS-CoV-2 PCR and antibody testing (every
29 2-4 weeks) and completed fortnightly questionnaires on symptoms and exposures. At
30 enrolment, participants were assigned to either the positive cohort (antibody positive or prior
31 PCR/antibody test positive) or negative cohort (antibody negative, not previously known to
32 be PCR/antibody positive). Potential reinfections were clinically reviewed and classified
33 according to case definitions (confirmed, probable, possible (subdivided by symptom-status))
34 depending on hierarchy of evidence. Individuals in the primary infection were excluded from
35 this analysis if infection was confirmed by antibody only. Reinfection rates in the positive
36 cohort were compared against new PCR positives in the negative cohort using a mixed
37 effective multivariable logistic regression analysis.

38 Findings: Between 18 June and 09 November 2020, 44 reinfections (2 probable, 42
39 possible) were detected in the baseline positive cohort of 6,614 participants, collectively
40 contributing 1,339,078 days of follow-up. This compares with 318 new PCR positive
41 infections and 94 antibody seroconversions in the negative cohort of 14,173 participants,
42 contributing 1,868,646 days of follow-up. The incidence density per 100,000 person days
43 between June and November 2020 was 3.3 reinfections in the positive cohort, compared
44 with 22.4 new PCR confirmed infections in the negative cohort. The adjusted odds ratio was
45 0.17 for all reinfections (95% CI 0.13-0.24) compared to PCR confirmed primary infections.
46 The median interval between primary infection and reinfection was over 160 days.

47 Interpretation: A prior history of SARS-CoV-2 infection was associated with an 83% lower
48 risk of infection, with median protective effect observed five months following primary
49 infection. This is the minimum likely effect as seroconversions were not included.

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56 1. **BACKGROUND**

57 There is an urgent need to better understand whether individuals who have recovered from
58 COVID-19 are protected from future SARS-CoV-2 infection.^{1,2} Establishing whether
59 reinfection is typically symptomatic or asymptomatic, whether reinfected individuals are
60 infectious to others and the expected duration of SARS-CoV-2 immunity from infection and
61 vaccination are key components of determining the future dynamics of SARS-CoV-2
62 circulation.

63 Reinfections have been reported internationally since June 2020, although they remain
64 uncommon.²⁻²¹ Large longitudinal cohort studies with regular testing are needed to
65 understand the rates of reinfection and their implications for policy by providing systematic
66 epidemiological, virological, immunologic and clinical data.²²

67 Over 90% of individuals infected with SARS-CoV-2 develop antibodies about one week after
68 symptoms onset, persisting for at least three months.^{23,24} High levels of neutralising
69 antibodies targeting SARS-CoV-2 Spike protein offer considerable protection against SARS-
70 CoV-2 reinfection, supported by data from common human coronaviruses and non-human
71 primate models and vaccine studies.²⁵⁻²⁹ Whilst the exact length of immunity conferred by
72 natural infection is still unknown, titres of neutralising antibodies against SARS-CoV-2 spike
73 protein were detectable for at least five months after primary infection.³⁰

74 A few studies to date have reported that individuals with SARS-CoV-2 antibodies are at
75 lower risk of clinical reinfection than antibody negative individuals.³¹⁻³³ However, given the
76 relatively small size of some of these cohorts and the lack of systematic SARS-CoV-2
77 molecular testing, the true population impact remains unknown.

78 The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) Study is a large, national,
79 multi-centre prospective cohort study of hospital healthcare workers across the National
80 Health Service in the United Kingdom, investigating whether the presence of antibody to

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81 SARS-CoV-2 (anti-SARS-CoV-2) is associated with a reduction in the subsequent risk of
82 symptomatic and asymptomatic reinfection over the next year.

83 This paper presents an interim analysis of the primary study objective, with data collected up
84 to 24 November 2020.

85

86 **2. METHODS**

87 **Study design and setting**

88 The SIREN study is a prospective cohort study among staff working in the publicly funded
89 hospitals (the National Health Service (NHS)) across the UK. The SIREN protocol is
90 described elsewhere.³⁴

91 **Participants**

92 All healthcare workers, support staff and administrative staff working at hospital sites
93 participating in SIREN, who could provide informed consent and anticipated remaining
94 engaged in follow-up for 12 months were eligible to join SIREN. Participants were excluded
95 from this analysis if they had no linked antibody or PCR data, no PCR tests after enrolment
96 or enrolled after 9 November 2020.

97 **Variables**

98 Questionnaires on symptoms and exposures were sent electronically at baseline and every
99 two weeks (Supplementary appendix); SARS-CoV-2 antibody (using the Roche cobas® or
100 Abbott immunoassay®) and Nucleic Acid Amplification Testing (NAAT), generally RT-PCR,
101 was conducted at enrolment and at regular intervals (PCR every two weeks, antibody every
102 four weeks). Testing was performed in the clinical laboratory at the site of participant
103 enrolment, using locally validated testing platforms.

104 **Cohort assignment at baseline**

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105 Participants were assigned to the positive cohort if they met one of the following criteria:
106 antibody positive on enrolment or antibody positive from prior clinical laboratory sample, with
107 or without prior PCR positive; antibody negative on enrolment with prior antibody positive,
108 with or without prior PCR positive; antibody negative on enrolment with a PCR positive result
109 prior to enrolment. Participants were assigned to the negative cohort if they had a negative
110 antibody test and no documented positive PCR test. Those in the negative cohort moved to
111 the positive cohort 21 days following a PCR positive test result or at the time of antibody
112 seroconversion with no positive PCR test.

113 **Reinfection case definitions**

114 The SIREN case definitions for reinfections have been described elsewhere and range from
115 confirmed to possible dependent on the strength of serological, genetic and virological
116 evidence.³⁶ A possible reinfection was defined as a participant with two PCR positive
117 samples 90 or more days apart (based on previous national surveillance analysis)³⁶ with
118 available genomic data or an antibody positive participant with a new positive PCR at least
119 four weeks after the first antibody positive result. A probable case additionally required
120 supportive quantitative serological data and/or supportive viral genomic data from
121 confirmatory samples.

122 We subcategorised possible reinfections by symptom status to highlight those with stronger
123 evidence and provide comparability with definitions used elsewhere.^{28,31} Participants
124 reporting any of cough, fever, anosmia or dysgeusia 14 days before or after their positive
125 PCR result were defined as having 'COVID-19 symptoms' and 'other potential COVID-19
126 symptoms' if reporting any other recognised symptoms listed in Appendix A.^{34,35}

127 **Data sources/measurement**

128 Individuals consented at enrolment for all their recorded results from the Public Health
129 England (PHE) national laboratory testing surveillance system from 1st February 2020 to be
130 included in this analysis.

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131 **Data management and linkage**

132 Personal identifiable information collected via the enrolment survey, completed by all SIREN
133 participants, was used to match participants to their NHS numbers, which were obtained
134 through the Demographic Batch Service (DBS). This information (forename, surname, date
135 of birth and NHS number) was used to link the SIREN survey data (enrolment and follow-up
136 survey) to results from all laboratory investigations (PCR and antibody data) held at PHE.
137 Automated data linkage was developed and run daily to extract new test results. All SIREN
138 data (survey and laboratory extracts) were sorted and matched in the SIREN SQL database.
139 Data were extracted from all sources on 24 November 2020.

140

141 **Detection of potential reinfections**

142 An SQL query was run on the SIREN database daily, to identify any participants who
143 'flagged' as a potential reinfection. This included participants who had two positive PCR
144 tests 90 days apart or antibody positive participants with a PCR positive test four weeks after
145 their first antibody positive date. In addition, sites were advised to report potential
146 reinfections.

147

148 **Bias**

149 Data were collected on potential confounders, including site and participant demographics to
150 permit adjustment in analysis. Questionnaires were piloted and formatted to reduce
151 misclassification bias. Recall bias was limited once enrolled by asking participants to
152 complete surveys two weekly for exposures and symptoms. Verification that sites were using
153 validated testing platforms and standardised criteria for reporting into SGSS was obtained
154 during site initiation.

155 **Study size**

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156 Recruitment will continue until 31 March 2021, recruiting up to 100,000 participants. The
157 study was originally powered to detect a difference in rate of infection between cohorts with
158 a sample size of 10,000 (25% estimated to be antibody positive at baseline), cumulative
159 incidence of 2% and immune efficacy of at least 50%.³⁴ The interim analysis was conducted
160 as the cumulative incidence in the total cohort reached 2%.

161 **Quantitative variables: Person time at risk**

162 Data was censored on 24 November 2020, with the following cohorts assigned.

- 163 a) Cohort susceptible to primary infection: From first antibody negative date or first PCR
164 positive date or seroconversion (if no PCR positive reported prior to seroconversion);
165 or if neither of these occurred, to censor date.
- 166 b) Cohort with prior infection: the earliest date for prior infection was taken as
167 whichever is first of the PCR positive result, onset of symptoms if there was no PCR
168 positive, or if neither is available the first positive antibody test.

169 **Statistical methods**

170 The cohort was described by their baseline cohort allocation. Participants with PCR positive
171 results in both negative and positive cohorts, were described in more detail. Cumulative
172 incidence, using the total number of participants in each cohort, and incidence density using
173 the total person time at risk was calculated for both cohorts and sub-categories and plotted
174 over time using PCR confirmation only. A mixed effects logistic regression analysis was
175 used to estimate odd ratios (OR) to measure the association between the exposure
176 (cohort allocation) and the binary outcome (PCR test result). The entry date used in this
177 analysis for all participants was the earliest antibody test. All PCR tests after the entry date
178 have been used, except PCR tests within 21 days of a positive PCR result. To account for
179 temporal changes in the background risk of infection, all tests were allocated to the calendar
180 week of the test date. These were categorised into nine groups; <week 31, then two-week
181 groups up to the final category of >week 44, allowing incidence over time to vary in a

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182 stepwise constant manner. Study site was fitted as a random effect to account for the
183 longitudinal nature of the study data, with age group, gender, ethnicity, staff group, and
184 region fitted as non-time varying fixed effects to account for their possible confounding
185 effect.³⁷ Analysis was conducted in STATA v15.1 (College Station, TX: StataCorp LLC).

186 **3. RESULTS**

187 From 18 June to 09 November 2020, 20,787 enrolled participants, with linked data on
188 antibody and PCR testing, were included in this analysis (figure 1). The baseline cohorts
189 assigned 6,614 (32%) to the positive cohort and 14,173 (68%) to the negative cohort. A full
190 description of the SIREN cohort and baseline risk factors for antibody positivity is published
191 separately.³⁵ Table 1 describes the SIREN participants by their baseline cohort assignment;
192 in summary the cohort was predominately female (n=17,487; 84%), white (n=18,304; 88%),
193 middle-aged (median age 45.9, interquartile range 35.8-53.6) and from clinical occupations
194 with representation from all English regions and two-thirds of acute hospital trusts.

195 The cohort had 129,189 PCR tests (17,538 before SIREN enrolment and 111,651 after
196 enrolment) and 91,165 antibody tests (13,867 before SIREN enrolment and 77,298 after
197 enrolment); median (and interquartile range) number of post enrolment PCR and antibody
198 tests were 5 (3-7) 3 (2-5) respectively.

199 Figure 2 describes the weekly total of new PCR positives (primary infection only) in SIREN
200 participants between March and November 2020 by baseline cohort assignment. It
201 demonstrates that PCR positivity in the positive cohort peaked in the first week of April in the
202 negative cohort was in the last week of October 2020.

203 By 24 November 2020, 409 new infections were detected in the negative cohort: 318 were
204 new PCR positive infections; 249 (79%) of these cases were symptomatic at infection, 196
205 (62%) with typical COVID-19 symptoms, and 53 (17%) with other symptoms; 40 (12%) were
206 asymptomatic and 28 (9%) did not complete a questionnaire at the time of their symptoms;

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207 94 were seroconversions in participants without a positive PCR test; these are not included
208 in this interim analysis.

209 Forty-four reinfections were identified, 15 (34%) were symptomatic: two defined as probable
210 (described in detail elsewhere³⁶), both symptomatic, and 42 possible; 13 symptomatic, two
211 (23%) of whom reported typical COVID-19 symptoms. Forty (both probable and 38 possible)
212 reinfections were antibody positive at enrolment; three had previously positive antibody tests
213 but two were antibody negative and one indeterminate on enrolment; and one individual
214 remained antibody negative but reported COVID-19 symptoms and a documented PCR
215 positive status in April 2020. Twenty-one (47.7%)(50%) of these individuals had historic PCR
216 positives from their primary infection, of whom 19 reported COVID-19 symptoms and two
217 other symptoms within 14 days of their positive test. Fourteen (31.8%) individuals (including
218 both probable cases) reported a history of COVID-19-like illness but did not have a PCR test
219 due to lack of availability at the time of their primary illness; 13 (92.9%) with typical COVID-
220 19 symptoms and one with other symptoms. Nine (20.5%) reported no history of any
221 potential COVID-19 related symptoms.

222 For the 32 reinfections providing a history of COVID-19 symptoms, used as a proxy to
223 estimate the date of their primary infection, the median interval between primary infection
224 and reinfection beyond 90 days was 172 days (90-227) and for the 21 reinfections with a
225 historic PCR positive test before enrolment, the median interval between the historic PCR
226 positive date and the reinfection PCR positive date was 162 days (95-223).

227 Between June and November 2020, the cumulative incidence of probable, symptomatic
228 possible and all reinfections in the positive cohort between June and November 2020 was
229 0.3, 2.3 and 6.7 per 1,000 participants respectively and incidence of symptomatic and all
230 new PCR infections in the negative cohort was 17.6 and 22.4 per 1,000 participants
231 respectively (Table 3). The incidence density per 100,000 days of follow up between June
232 and November 2020 in the positive cohort was 3 .3 reinfections and in the negative cohort
233 was 17.0 new PCR positive infections per 100,000 days of follow-up. Figure 3 describes the

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234 cumulative incidence of new episode PCR positive tests per cohort demonstrating the higher
235 cumulative incidence in the negative cohort reaching 20 per 1000 compared 5 per 1000
236 cases in the positive cohort.

237 We estimated the relative odds for reinfections in the positive cohort, with separate analyses
238 for each reinfection definition described above, compared to new PCR positive infections in
239 our negative cohort between SIREN enrolment and 24 November 2020 (Table 4, annex B
240 Tables Bi.-Biii).

241 Restricting reinfections to probable reinfections only, we estimated that between June and
242 November 2020, participants in the positive cohort had 99% lower odds of probable
243 reinfection, adjusted OR (aOR) 0.01 (95% CI 0.00-0.03). Restricting reinfections to those
244 who were symptomatic we estimated participants in the positive cohort had 95% lower odds
245 of reinfection, aOR 0.08 (95% CI 0.05-0.13). Using our most sensitive definition of
246 reinfections, including all those who were possible or probable the adjusted odds ratio was
247 0.17 (95% CI 0.13-0.24).

248 The two approaches to account for temporal changes in incidence provided very similar
249 estimates, we have opted to present results from the model with calendar time categorised.
250 This also shows how the probability of exposure to an infectious individual has changed over
251 time in a piecewise constant manner, increasing over time as incidence of new infections in
252 the population increased in September and October 2020.

253

254 **4. DISCUSSION**

255 We have presented the interim findings after five months of follow-up from the SIREN study,
256 a unique large-scale multi-centre prospective cohort study of healthcare staff undergoing
257 frequent asymptomatic testing, powered to detect and characterise reinfections and estimate
258 the protective effect of SARS-CoV-2 antibodies.

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259 We have detected two probable reinfections (both symptomatic with high viral loads,
260 genome sequencing demonstrating phylogenetic relatedness to concurrently circulating
261 strains, and a boosted antibody response), which have been characterised and reported
262 separately,³⁶ and 42 possible reinfections in our positive cohort. This compares with 318
263 new PCR positive infections, 249 of whom were symptomatic, 78% with typical COVID-19
264 symptoms, in our negative cohort. Using a symptomatic case definition aligned with positive
265 PCR results, previous infection reduced the odds of infection by at least 90% (aOR 0.06 with
266 95%CI of 0.03 to 0.09) and even when we included all possible and probable reinfections
267 reduced the odds of reinfection by at least 75% [aOR 0.17 (95% CI 0.13-0.24)]

268 We believe this is the minimum likely impact as the curve in the positive cohort was gradual
269 throughout, indicating some of these potential reinfections were likely residual RNA detection
270 at low population prevalence rather than true reinfections. In the negative cohort the gradient
271 was gradual up to around day 100 and has then accelerated, broadly coinciding with the
272 period when community prevalence increased rapidly.³⁸ In addition, we did not include 94
273 seroconversions in the negative cohort, as these seroconversions were not detected by PCR
274 and we cannot currently say whether a similar rate of undetected infections occurred in the
275 positive cohort. None of the reinfections we have identified are confirmed by our stringent
276 case definitions; most we only consider possible and are undergoing further serological
277 investigation. Investigations have been restricted by the limited availability of data and
278 samples from historic infections, with most swabs discarded without sequencing, preventing
279 the genomic comparison between infection episodes required to confirm a reinfection. This
280 highlights the importance of SIREN, through which we are ensuring the data collection and
281 characterisation of new infections, to build a stronger base to investigate and confirm future
282 reinfections. Our use of hierarchical case definitions identifies cases with stronger evidence,
283 and allows us present the range of potential reinfection scenarios.

284 Another limitation is measurement error capturing the primary infection onset date for
285 positive cohort participants without a PCR positive test associated with their primary

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286 episode. This introduces imprecision into both our person time at risk, and consequently
287 reinfection rates, and our estimated intervals between primary infection episodes and
288 reinfections. For those who were symptomatic in their primary episode we have used their
289 self-reported COVID-19 symptom onset date as a proxy, which may be subject to recall bias.
290 We have introduced validation rules here to reduce this, excluding onset dates before March
291 2020. However, for participants with asymptomatic or non-COVID-19 symptomatic primary
292 infections, we are reliant on using their first antibody positive date. We are therefore not
293 capturing all the time they were susceptible to reinfection, reducing our overall follow-up time
294 for this cohort, and thus inflating our reinfection rates and reducing our intervals between
295 infection episodes.

296 As the cohort assignment has been determined by testing at SIREN sites, which use a range
297 of testing platforms and assays, there is the possibility of misclassification bias. We have
298 included participants in the positive cohort who had a prior positive PCR test, irrespective of
299 their antibody status. Some of those PCR results, especially early in the epidemic, may
300 have been false positives or laboratory contamination episodes, particularly given Ct/RLU
301 values are not available. We aim to retest all baseline serum samples within PHE, using
302 both S and N target assays in order to give each participant a validated quantitative baseline
303 antibody result. This will inform future analyses and may lead to changes to the cohort
304 assignment presented.

305 Finally, this interval analysis is presented prior to the widespread emergence and spread of
306 the B.1.1.7 lineage (VOC202012/01) with multiple non-synonymous spike mutations including
307 N501Y; the impact of this lineage on future protection remains undetermined and will be
308 evaluated.

309 Our results are consistent with the findings from other smaller studies of decreased
310 incidence of PCR positivity in antibody positive individuals.^{31,39} Another prospective cohort of
311 healthcare workers recently reported the incidence of new positive PCR-confirmed infections
312 to be lower among seropositive than seronegative participants (n=3/1,246 vs. n=165/11,052,

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313 an incidence density of 2.1 and 8.6/100,000 days at risk respectively).³¹ None of the three
314 potential reinfections were symptomatic.

315 The recent SARS-CoV-2 vaccination trials have typically investigated protection from
316 symptomatic infection. The ChAdOx1 trial reported protection against symptomatic infection
317 of between 70.4% and 90%, and the BNT162b2 vaccine phase 3 results report 95%
318 protection over two and three months of follow-up respectively.^{28,29} Our findings, after a
319 longer period of follow-up, of 94% lower odds of symptomatic infection, demonstrate
320 equivalent, or higher protection from natural infection, both for symptomatic and
321 asymptomatic infection.

322 After five months of follow-up, this large observational study has found that prior SARS-CoV-
323 2 infection protects most individuals against reinfection for at least five months. We have
324 identified and investigated more potential reinfections than reported in the global literature to
325 date, supporting the value of large prospective cohort studies such as SIREN. This study
326 supports the hypothesis that primary infection with SARS-CoV-2 provides a high degree of
327 immunity to repeat infection in the short to medium term; with similar levels of prevention of
328 symptomatic infection as current licensed vaccines for working age adults. Primary infection
329 also reduces the risk of asymptomatic infection and thus onward transmission; this is
330 particularly important in the healthcare was considered as a potential driver for ongoing
331 community transmission in Wave 1 in the UK.⁴⁰ This increases the likelihood that this may
332 also be attainable by vaccine induced immunity. Further detailed studies on the longevity of
333 antibody responses, assessment of reinfection rates under the challenge of the new lineage,
334 and the impact of all COVID-19 vaccines introduced in the UK are underway in this cohort.

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347 **6. Trial Registration**

348 IRAS ID 284460, HRA and Health and Care Research Wales approval granted 22 May
349 2020. Trial ID: ISRCTN11041050.

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492 **TABLES**

493 **Table 1: Demographics of SIREN participants by baseline cohort allocation,**
 494 **participants enrolled 18 June to 09 November 2020 (n=20,787)**

Characteristics	Positive cohort	Negative cohort	All Participants
	n (%)	n (%)	n (%)
Gender			
Female	5452 (82.4)	12035 (84.9)	17487 (84.1)
Male	1152 (17.4)	2121 (15.0)	3273 (15.7)
Other	10 (0.2)	17 (0.1)	27 (0.1)
Age			
Median [IQR]	46 [35.1-54]	45.9 [36-53.9]	45.9 [35.8-53.6]
Range	18.6-78.4	18.6-84.3	18.6-84.3
Ethnicity			
White	5607 (84.8)	12697 (89.6)	18304 (88.1)
Mixed Race	558 (8.4)	780 (5.5)	1338 (6.4)
Asian	188 (2.8)	226 (1.6)	414 (2.0)
Black	102 (1.5)	211 (1.5)	313 (1.5)
Chinese	111 (1.7)	161 (1.1)	272 (1.3)
Other Ethnic Group	38 (0.6)	74 (0.5)	112 (0.5)
Prefer not to say	10 (0.2)	24 (0.2)	34 (0.2)
Staff group			
Nursing/Healthcare Assistant	2964 (44.8)	5805 (41.0)	8769 (42.2)
Administrative/Executive	885 (13.4)	2311 (16.3)	3196 (15.4)
Doctor	793 (12)	1423 (10)	2216 (10.7)
Specialist staff	340 (5.1)	783 (5.5)	1123 (5.4)
Healthcare Scientist	176 (2.7)	548 (3.9)	724 (3.5)
Midwife	163 (2.5)	379 (2.7)	542 (2.6)
Pharmacist	78 (1.2)	192 (1.4)	270 (1.3)
Estates/Porters/Security	56 (0.8)	103 (0.7)	159 (0.8)
Other	1159 (17.5)	2629 (18.5)	3788 (18.2)
Medical conditions			
No medical conditions	4944 (74.8)	10590 (74.7)	15534 (74.7)
One to two medical conditions	1635 (24.7)	3512 (24.8)	5147 (24.8)
Over two medical conditions	35 (0.5)	71 (0.5)	106 (0.5)
Region			
South West	1016 (15.4)	3762 (26.5)	4778 (23)
North West	1074 (16.2)	1730 (12.2)	2804 (13.5)
London	1031 (15.6)	1570 (11.1)	2601 (12.5)
South East	748 (11.3)	1685 (11.9)	2433 (11.7)
East Midlands	759 (11.5)	1586 (11.2)	2345 (11.3)
East of England	553 (8.4)	1516 (10.7)	2069 (10)
West Midlands	710 (10.7)	977 (6.9)	1687 (8.1)
Yorkshire and the Humber	541 (8.2)	1040 (7.3)	1581 (7.6)
North East	182 (2.8)	307 (2.2)	489 (2.4)
All Participants	6614 (31.8)	14173 (68.2)	20787 (100.0)

Table 2: Characteristics of reinfections and new infections detected in SIREN participants up to 24 November 2020, stratified by case definition (n=362)

	Positive cohort			Negative cohort
	Probable n (%)	Symptomatic possible n (%)	All probable/ possible n (%)	New PCR+ n (%)
Gender				
Female	2 (100)	11 (84.6)	36 (81.8)	261 (82.1)
Male	0 (0)	2 (15.4)	8 (18.2)	56 (17.6)
Other	0 (0)	0 (0)	0 (0)	1 (0.3)
Age				
Median (range)	41.5 (37-46)	46 (25-58)	48.5 (23-63)	45.3 (19-70)
Antibody status at baseline				
Positive	2 (100)	12 (92.3)	40 (90.9)	0 (0)
Negative	0 (0)	1 (7.7)	3 (6.8)	310 (97.5)
Indeterminate/not available	0 (0)	0 (0)	1 (2.3)	8 (2.5)
Reinfection PCR semi quantitative values (CT/RLU)				
CT range (n)	21-24 (2)	13-37 (5)	13-45 (16)	-
RLU range (n)	-	587-1193 (6)	591-1260 (20)	-
Symptom status +/-14 days reinfection PCR+				
COVID-19 symptoms	1 (50)	3 (23.1)	4 (9.1)	196 (61.6)
Any other symptoms	1 (50)	10 (76.9)	11 (25)	53 (16.7)
No symptoms	0 (0)	0 (0)	21 (47.7)	40 (12.6)
Not known	0 (0)	0 (0)	8 (18.2)	29 (9.1)
Time interval in days – median (range); n				
Symptom onset first episode to reinfection PCR	212 (197-227); 2	166 (90-223); 10	169 (90-227); 32	-
First positive PCR to reinfection PCR	-	155 (95-201); 7	162 (95-223); 21	-
First antibody positive to reinfection PCR	63 (62-64); 2	110 (35-136); 12	101.5 (35-174); 42*	-
Total	2	13	44	318

*One participant never antibody positive, one participant first reported as antibody positive on the same date as reinfection PCR date.

Table 3: Frequency of new infections and possible/probable reinfections by cohort, characterised by symptoms within 14 days (pre/post) of PCR positive date and exposures in preceding 14 days (n=362)

	Positive cohort					Negative cohort				
	n	Denominator		Incidence		n	Denominator		Incidence	
		Total participants	Person time at risk (days)	Cumulative (per 1000)	Density (per 100,000)		Total participants	Person time at risk (days)	Cumulative (per 1000)	Density (per 100,000)
Reinfections						New PCR				
Probable	2	6614	1,339,078	0.3	0.1	-	-	-	-	-
Probable AND Symptomatic possible	15	6614	1,339,078	2.3	1.1	249	14,173	1,868,646	17.6	13.3
All events	44	6614	1,339,078	6.7	3.3	318	14,173	1,868,646	22.4	17.0

Table 4: Univariable and multivariable analysis of risk of infection by cohort during SIREN follow-up, using a range of reinfection case definitions, between 18 June and 24 November 2020

Reinfections	n	OR (95% CI)	p-value	aOR* (95% CI)	p-value
Probable	2	0.01 (0.00-0.03)	<0.01	0.01 (0.00-0.03)	<0.01
Probable and symptomatic possible	15	0.06 (0.03-0.10)	<0.01	0.06 (0.03-0.09)	<0.01
Probable and all possible	44	0.17 (0.13-0.24)	<0.01	0.17 (0.12-0.23)	<0.01

Note: odds ratio (OR); adjusted odds ratio (aOR); aOR adjusted for week group: reference group week 25 to 30; remaining week groups: week 31 to 47 (two-week time-periods)

FIGURES

Figure 1: Flow diagram describing participant flow and exclusion criteria for participants enrolled in SIREN between 18 June and 09 November 2020

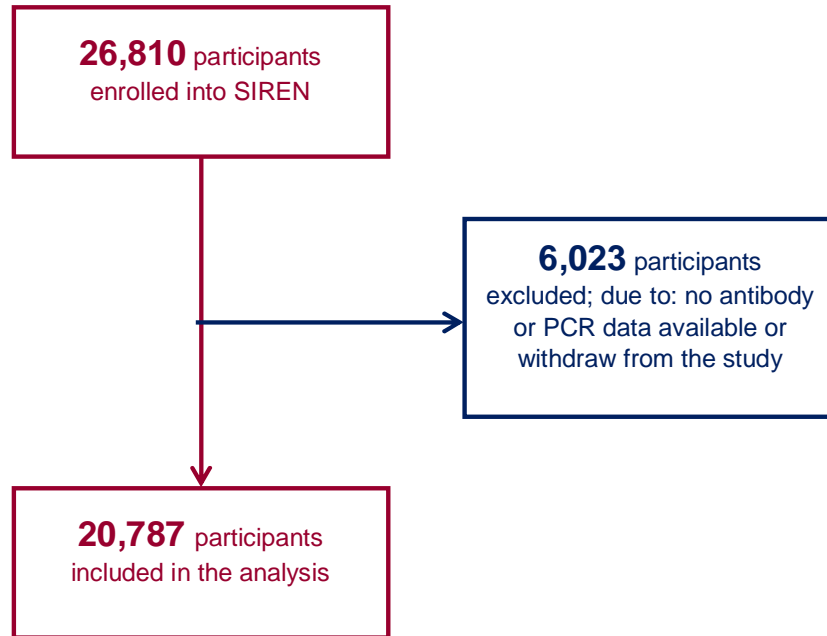
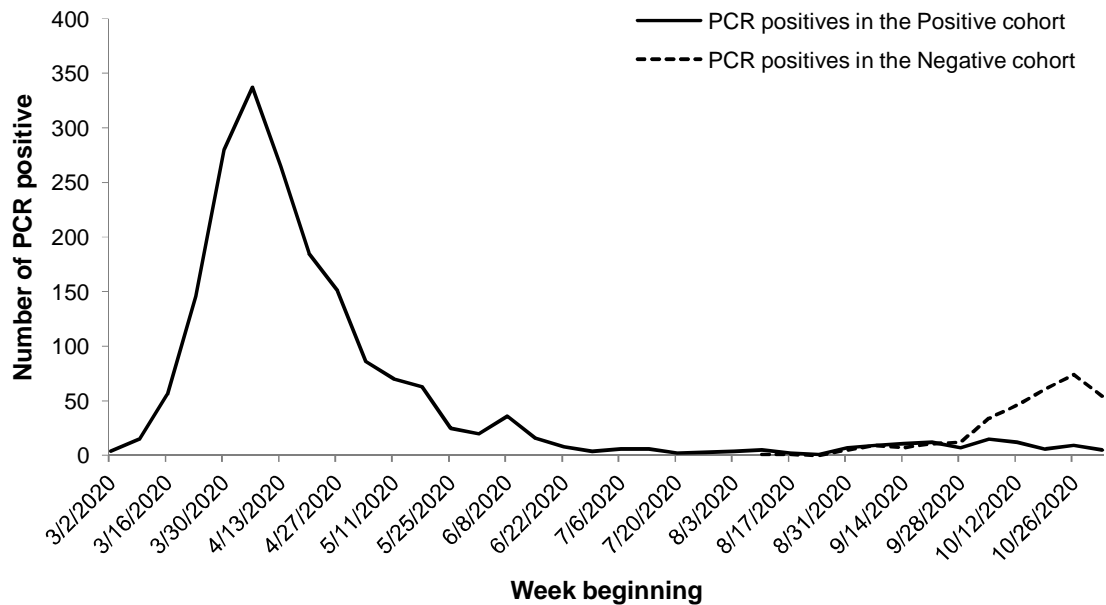
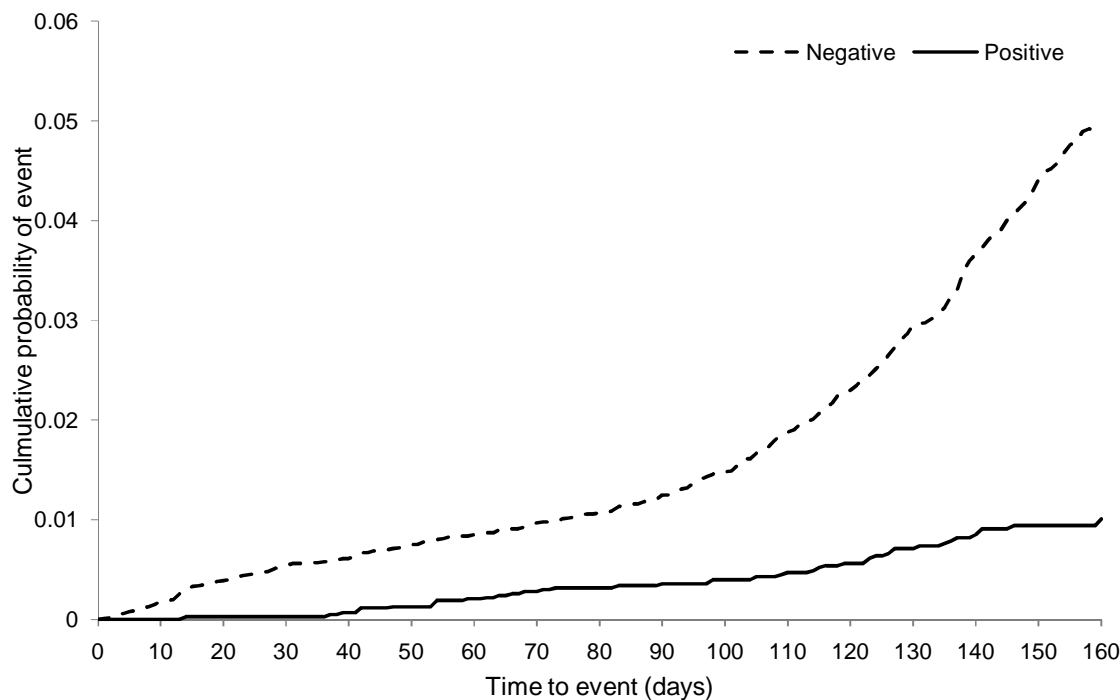


Figure 2: Weekly frequency of SIREN participants with a first PCR positive test result by baseline cohort assignment, March to 24 November 2020



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Figure 3: Time to PCR positive result by cohort in SIREN participants, detected up to 24 November 2020



Note: 318 PCR positive results were reported in the negative cohort; 44 PCR reinfections (probable and possible reinfections) were detected in the positive cohort during SIREN follow-up to 24 November 2020. In the positive cohort follow-up time started from date of primary PCR positive, or primary symptom onset (if no historic PCR positive and history of COVID-19 symptoms reported) or date first antibody positive. In the negative cohort follow-up started at the date of first negative antibody result. Follow-up time has been truncated at 160 days due to the size of the risk-sets becoming very small

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Appendix A. Symptom list in questionnaire

Cough, Fever, Anosmia, Dysgeusia, Sore throat, runny nose, headache, muscle aches, fatigue, diarrhoea, vomiting, itchy red patches.

Appendix B.

Table Bi: Multivariable analysis of risk of infection by cohort during SIREN follow-up, probable reinfections, between 18 June and 24 November 2020 (n=2)

Characteristics	OR (95% CI)	p-value
Positive	0.01 (0.00-0.03)	<0.01
Week group		
25 to 30	-	-
31 to 32	0.12 (0.04-0.32)	<0.01
33 to 34	0.14 (0.06-0.32)	<0.01
35 to 36	0.27 (0.15-0.49)	<0.01
37 to 38	0.48 (0.31-0.75)	<0.01
39 to 40	0.40 (0.25-0.62)	<0.01
41 to 42	0.99 (0.68-1.45)	0.97
43 to 44	1.05 (0.73-1.52)	0.79
45 to 47	0.20 (0.12-0.32)	0.00
Age group		
18 to 24	-	-
25 to 34	0.70 (0.44-1.11)	0.13
35 to 44	0.46 (0.29-0.73)	<0.01
45 to 54	0.64 (0.41-1.00)	0.05
55 to 64	0.48 (0.30-0.78)	<0.01
Over 65	0.25 (0.07-0.83)	0.02
Gender		
Male	-	-
Female	0.83 (0.63-1.09)	0.18
Other	1.40 (0.18-10.60)	0.74
Ethnicity		
White	-	-
BAME	1.51 (1.12-2.04)	0.01
Staff group		
Nursing/Healthcare Assistant	-	-

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Doctor	0.66 (0.45-0.96)	0.03
Midwife	0.83 (0.45-1.54)	0.56
Administrative/Executive	0.75 (0.55-1.01)	0.06
Specialist staff	0.79 (0.50-1.24)	0.30
Estates/Porters/Security	2.08 (0.95-4.55)	0.07
Pharmacist	0.89 (0.41-1.93)	0.76
Healthcare Scientist	0.48 (0.26-0.89)	0.02
Other	0.73 (0.56-0.96)	0.03
Region		
East Midlands	-	-
East of England	0.52 (0.25-1.07)	0.07
London	0.34 (0.17-0.68)	<0.01
North East	1.98 (0.75-5.24)	0.17
North West	1.53 (0.86-2.74)	0.15
South East	0.58 (0.31-1.09)	0.09
South West	0.32 (0.17-0.59)	<0.01
West Midlands	1.64 (0.87-3.10)	0.13
Yorkshire and the Humber	1.77 (0.93-3.36)	0.08

Table Bii: Multivariable analysis of risk of infection by cohort during SIREN follow-up, probable and symptomatic possible reinfections, between 18 June and 24 November 2020 (n=15)

Characteristics	OR (95% CI)	p-value
Positive	0.06 (0.03-0.09)	<0.01
Week group		
25 to 30	-	-
31 to 32	0.11 (0.04-0.31)	<0.01
33 to 34	0.16 (0.07-0.35)	<0.01
35 to 36	0.28 (0.16-0.50)	<0.01
37 to 38	0.48 (0.31-0.75)	<0.01
39 to 40	0.39 (0.25-0.61)	<0.01
41 to 42	1.03 (0.71-1.49)	0.89
43 to 44	1.05 (0.73-1.51)	0.80
45 to 47	0.20 (0.13-0.32)	<0.01
Age group		
18 to 24	-	-
25 to 34	0.72 (0.45-1.13)	0.15
35 to 44	0.49 (0.31-0.77)	<0.01
45 to 54	0.68 (0.44-1.06)	0.09

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	55 to 64	0.50 (0.31-0.81)	<0.01
	Over 65	0.25 (0.07-0.84)	0.02
Gender			
	Male	-	-
	Female	0.84 (0.64-1.10)	0.20
	Other	1.39 (0.18-10.46)	0.75
Ethnicity			
	White	-	-
	BAME	1.50 (1.12-2.02)	0.01
Staff group			
	Nursing/Healthcare Assistant	-	-
	Doctor	0.67 (0.46-0.97)	0.04
	Midwife	0.83 (0.45-1.53)	0.55
	Administrative/Executive	0.78 (0.58-1.04)	0.09
	Specialist staff	0.82 (0.53-1.28)	0.39
	Estates/Porters/Security	2.02 (0.93-4.42)	0.08
	Pharmacist	0.90 (0.41-1.96)	0.79
	Healthcare Scientist	0.52 (0.29-0.95)	0.03
	Other	0.74 (0.56-0.97)	0.03
Region			
	East Midlands	-	-
	East of England	0.60 (0.30-1.19)	0.14
	London	0.33 (0.17-0.64)	<0.01
	North East	1.88 (0.74-4.78)	0.19
	North West	1.53 (0.87-2.66)	0.14
	South East	0.59 (0.32-1.09)	0.09
	South West	0.32 (0.18-0.57)	<0.01
	West Midlands	1.60 (0.87-2.95)	0.13
	Yorkshire and the Humber	1.67 (0.90-3.08)	0.10

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Table Biii: Multivariable analysis of risk of infection by cohort during SIREN follow-up, probable and all possible reinfections, between 18 June and 24 November 2020 (n=44)

Characteristics	OR (95% CI)	p-value	
	Positive	0.17 (0.12-0.23)	<0.01
Week group			
	25 to 30	-	-
	31 to 32	0.13 (0.05-0.32)	<0.01
	33 to 34	0.20 (0.10-0.40)	<0.01
	35 to 36	0.31 (0.18-0.52)	<0.01
	37 to 38	0.46 (0.30-0.70)	<0.01
	39 to 40	0.39 (0.25-0.59)	<0.01
	41 to 42	0.97 (0.68-1.38)	0.87
	43 to 44	0.96 (0.68-1.36)	0.81
	45 to 47	0.20 (0.13-0.31)	<0.01
Age group			
	18 to 24	-	-
	25 to 34	0.67 (0.43-1.04)	0.07
	35 to 44	0.48 (0.31-0.75)	<0.01
	45 to 54	0.67 (0.44-1.03)	0.07
	55 to 64	0.52 (0.33-0.81)	<0.01
	Over 65	0.24 (0.07-0.79)	0.02
Gender			
	Male	-	-
	Female	0.84 (0.65-1.08)	0.18
	Other	1.32 (0.18-9.85)	0.79
Ethnicity			
	White	-	-
	BAME	1.47 (1.11-1.95)	0.01
Staff group			
	Nursing/Healthcare Assistant	-	-
	Doctor	0.72 (0.51-1.02)	0.07
	Midwife	0.78 (0.42-1.43)	0.42
	Administrative/Executive	0.73 (0.55-0.97)	0.03
	Specialist staff	0.86 (0.56-1.31)	0.48
	Estates/Porters/Security	1.87 (0.86-4.07)	0.11
	Pharmacist	0.90 (0.42-1.96)	0.79
	Healthcare Scientist	0.51 (0.28-0.91)	0.02
	Other	0.72 (0.56-0.94)	0.02
Region			
	East Midlands	-	-

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East of England	0.58 (0.30-1.10)	0.10
London	0.36 (0.20-0.67)	<0.01
North East	1.76 (0.73-4.25)	0.21
North West	1.50 (0.90-2.52)	0.12
South East	0.60 (0.34-1.05)	0.07
South West	0.36 (0.21-0.62)	<0.01
West Midlands	1.55 (0.88-2.73)	0.13
Yorkshire and the Humber	1.60 (0.90-2.84)	0.11

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