SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN)

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Summary

Background Increased understanding of whether individuals who have recovered from COVID-19 are protected from future SARS-CoV-2 infection is an urgent requirement. We aimed to investigate whether antibodies against SARS-CoV-2 were associated with a decreased risk of symptomatic and asymptomatic reinfection.

Methods A large, multicentre, prospective cohort study was done, with participants recruited from publicly funded hospitals in all regions of England. All health-care workers, support staff, and administrative staff working at hospitals who could remain engaged in follow-up for 12 months were eligible to join The SARS-CoV-2 Immunity and Reinfection Evaluation study. Participants were excluded if they had no PCR tests after enrolment, enrolled after Dec 31, 2020, or had insufficient PCR and antibody data for cohort assignment. Participants attended regular SARS-CoV-2 PCR and antibody testing (every 2–4 weeks) and completed questionnaires every 2 weeks on symptoms and exposures. At enrolment, participants were assigned to either the positive cohort (antibody positive, or previous positive PCR or antibody test) or negative cohort (antibody negative, no previous positive PCR or antibody test). The primary outcome was a reinfection in the positive cohort or a primary infection in the negative cohort, determined by PCR tests. Potential reinfections were clinically reviewed and classified according to case definitions (confirmed, probable, or possible) and symptom-status, depending on the hierarchy of evidence. Primary infections in the negative cohort were defined as a first positive PCR test and seroconversions were excluded when not associated with a positive PCR test. A proportional hazards frailty model using a Poisson distribution was used to estimate incidence rate ratios (IRR) to compare infection rates in the two cohorts.

Findings From June 18, 2020, to Dec 31, 2020, 30 625 participants were enrolled into the study. 51 participants withdrew from the study, 4913 were excluded, and 25 661 participants (with linked data on antibody and PCR testing) were included in the analysis. Data were extracted from all sources on Feb 5, 2021, and include data up to and including Jan 11, 2021. 155 infections were detected in the baseline positive cohort of 8278 participants, collectively contributing 2 047 113 person-days of follow-up. This compares with 1704 new PCR positive infections in the negative cohort of 17 383 participants, contributing 2 971 436 person-days of follow-up. The incidence density was 7·6 reinfections per 100 000 person-days in the positive cohort, compared with 57·3 primary infections per 100 000 person-days in the negative cohort, between June, 2020, and January, 2021. The adjusted IRR was 0·159 for all reinfections (95% CI 0·13–0·19) compared with PCR-confirmed primary infections. The median interval between primary infection and reinfection was more than 200 days.

Interpretation A previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. This time period is the minimum probable effect because seroconversions were not included. This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals.

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Introduction

Knowledge of whether individuals who have recovered from COVID-19 are protected from future SARS-CoV-2 infection is an urgent requirement.[1,2] Establishing whether reinfection is typically symptomatic or asymptomatic, whether reinfected individuals are infectious to others, and the expected duration of SARS-CoV-2 immunity from infection and vaccination are key components of determining the future dynamics of SARS-CoV-2 circulation.

Reinfections have been reported internationally since June, 2020, although they remain uncommon.[2–21] Large longitudinal cohort studies with regular testing are

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See Online for appendix 1

Research in context

Evidence before this study

By Nov 25, 2020, 24 cases of potential reinfection with SARS-CoV-2 virus had been reported in scientific literature globally. A systematic search of Embase, MEDLINE, the WHO COVID-19 literature database, and preprint servers on Oct 23, 2020, found 395 articles of interest published in English. Detailed search terms for the databases are presented in appendix 1 (p 1). After title and abstract screening, 47 articles were obtained in full and 15 reported potential SARS-CoV-2 reinfections. An additional article that contained a case was added from reference list searches of these articles. Subsequent rolling research alerts (up to Nov 25, 2020), using the same search strategies, identified an additional 139 articles, 38 of which passed title and abstract screening and were obtained in full. Three of these articles reported potential cases of SARS-CoV-2 reinfection that had not been reported previously, contributing to a total of 19 manuscripts that reported 24 cases of potential reinfection collectively. According to our reinfection case definitions reported previously, 18 of the 24 cases would be considered to have the evidence required to support reinfection: three cases from the literature had enough evidence to be classed as probable and 15 cases would be classed as possible. The remaining cases did not have enough evidence to be classed as a reinfection and instead were classed as intermittent PCR positivity.

Added value of this study

In comparison, by Jan 11, 2021, SIREN had detected two cases meeting probable and 153 cases meeting possible SARS-CoV-2 reinfection definition from a cohort of 8278 participants that have previously been infected with SARS-CoV-2. Although the report and study of individual cases of SARS-CoV-2 reinfection is important to build our understanding of the body's response to reinfection, large cohort studies are essential to gain more information about reinfection rate and the characteristics that predispose to reinfection. The SARS-CoV-2 Immunity and Reinfection Evaluation study is powered to achieve such objectives, with a large proportion of seropositive participants from enrolment, and provide robust answers to drive policy.

Implications of all the available evidence

We are at a precarious point of the SARS-CoV-2 epidemic in the UK, with cases due to new strains emerging across the nation while social restrictions are in the process of being lifted. Although vaccines have started to become more widely available, there are several difficult months ahead and the longevity of natural and vaccine-associated immunity is uncertain, particularly in emerging strains. This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals. The importance of understanding the nature and rate of SARS-CoV-2 reinfection to guide non-pharmaceutical interventions and public health control measures is essential in this evolving pandemic.

needed to understand the rates of reinfection and their implications for policy by providing systematic epidemiological, virological, immunological, and clinical data.[22]

More than 90% of individuals infected with SARS-CoV-2 develop antibodies about 1 week after symptom onset, persisting for at least 3 months.[23,24] High concentrations of neutralising antibodies targeting the SARS-CoV-2 spike protein offer considerable protection against SARS-CoV-2 reinfection, supported by data from common human coronaviruses and non-human primate models and vaccine studies.[25–29] Although the exact length of immunity conferred by natural infection is still unknown, titres of neutralising antibodies against the SARS-CoV-2 spike protein were detectable for at least 5 months after primary infection.[23]

A few studies to date have reported that individuals with SARS-CoV-2 antibodies are at lower risk of clinical reinfection than are antibody-negative individuals.[23,30–32] However, given the relatively small size of some of these cohorts and the lack of systematic SARS-CoV-2 molecular testing, the true population effect remains unknown.

The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study is a large, national, multicentre prospective cohort study of hospital health-care workers across the National Health Service (NHS) in the UK, which investigated whether the presence of antibodies against SARS-CoV-2 was associated with a reduction in the subsequent risk of symptomatic and asymptomatic reinfection over the 12 months of follow-up. This Article presents an interim analysis of the primary study objective, with data collected up to Jan 11, 2021.

Methods

Study design and participants

The SIREN study is a prospective cohort study among staff working in the NHS publicly funded hospitals across the UK. Although recruitment of participants from Scotland and Northern Ireland began before Dec 31, 2020, their testing data was not available to the Public Health England study team at the time of this analysis and, therefore, they were excluded. All health-care workers, support staff, and administrative staff working at hospital sites participating in SIREN, who could provide written informed consent and anticipated remaining engaged in follow-up for 12 months were eligible to join SIREN. Participants were excluded from this analysis if they had no PCR tests after enrolment, enrolled after Dec 31, 2020, or had insufficient PCR and antibody data to complete cohort assignment. Individuals provided consent at enrolment for all of their recorded results from the Public Health England national laboratory testing surveillance

system from Feb 1, 2020, to be included in this analysis. Recruitment of Welsh participants began in 2021. The SIREN protocol has previously been described.[33] Ethical approval was granted by Berkshire Research Ethics Committee, and Health Research Authority and Health and Care Research Wales.

Procedures

Questionnaires on symptoms and exposures were sent electronically at baseline and every 2 weeks. SARS-CoV-2 antibody testing and Nucleic Acid Amplification Testing (NAAT) with real-time PCR (rtPCR) was done at enrolment and at regular intervals (PCR every 2 weeks, antibody testing every 4 weeks). Most sites used rtPCR; however, a small number of sites used Loop-mediated isothermal amplification testing or Rapid Testing with rtPCR to confirm positive results. For NAAT, self-sampled swabs or swabs taken by a trained professional were accepted (including anterior nasal swabs or combined nose and oropharyngeal swabs). SARS-CoV-2 serology was done with locally validated assays. Testing was done in the clinical laboratory at the site of participant enrolment, with locally validated testing platforms. Index of multiple deprivation, a measure of neighbourhood relative deprivation calculated by the Office of National Statistics, was obtained through linkage on participant postcode. COVID-19 vaccination was introduced into this cohort in December, 2020, and data on vaccination status was provided by participants through the questionnaires and through linkage to the National Immunisation Management System. We generated a binary variable to delineate follow-up time after a participant had been vaccinated for 21 days or more. The B.1.1.7 variant emerged and spread during the study period, and the effect of this variant was included in our analysis by creating a binary variable of when the S-Gene Target Failure (SGTF) PCR, used to identify the B.1.1.7 variant in the laboratory network, accounted for 50% or more of the positive results for each region.[34] The SGTF PCR testing was introduced to specific laboratories in England only, termed Pillar 2 laboratories, which are large hospital laboratories established specifically for the COVID-19 response for the purpose of community testing.

Participants were assigned to the positive cohort if they met one of the following criteria: antibody positive on enrolment or antibody positive from previous clinical laboratory samples, with or without a previous positive PCR test; antibody negative on enrolment with a positive PCR result before enrolment. Participants were assigned to the negative cohort if they had a negative antibody test and no documented previous positive PCR or antibody test. Participants with linked negative PCR tests but no linked antibody data were excluded from this analysis because data were insufficient to assign them to a cohort.

The SIREN case definitions for reinfections range from confirmed to possible, dependent on the strength of serological, genetic, and virological evidence (appendix 1 p 2). A possible reinfection was defined as a participant with two positive PCR samples 90 or more days apart (based on previous national surveillance analysis) or an antibody positive participant with a new positive PCR test at least 4 weeks after the first antibody-positive result. Participants with recurrent positive PCR results less than 90 days apart who developed antibodies during this interval were not considered possible reinfections regardless of whether the latest positive PCR result was 4 weeks after the seroconversion. A probable case additionally required supportive quantitative serological data or supportive viral genomic data from samples available. We subcategorised possible reinfections by symptom status to emphasise those with stronger evidence and provide comparability with definitions used elsewhere.[28,30] Participants reporting cough, fever, anosmia, or dysgeusia 14 days before or after their positive PCR result were defined as having COVID-19 symptoms, and if patients reported a sore throat, runny nose, headache, muscle aches, fatigue, diarrhoea, vomiting, or itchy red patches they were defined as having other potential COVID-19 symptoms.

For data management and linkage, personal identifiable information collected via the enrolment survey completed by all SIREN participants was used to match participants to their NHS numbers, which were obtained through the Demographic Batch Service. This information (forename, surname, date of birth, and NHS number) was used to link the SIREN survey data (enrolment and follow-up survey) to results from all laboratory investigations (PCR and antibody data) held at Public Health England. Automated data linkage was developed and run daily to extract new test results. All SIREN data (survey and laboratory extracts) were sorted and matched in the SIREN Structured Query Language (SQL) database.

An SQL query was run on the SIREN database daily, to identify any participants who might be categorised as a potential reinfection. This included participants who had two positive PCR tests 90 days apart or antibody-positive participants with a positive PCR test 4 weeks after their first antibody-positive date. Sites were advised to report potential reinfections.

Data were collected on potential confounders, including site and participant demographics, to permit adjustment in analysis. Questionnaires were piloted and formatted to reduce misclassification bias. Recall bias was limited once participants were enrolled by asking them to complete surveys every 2 weeks for exposures and symptoms. Verification that sites were using validated testing platforms and standardised criteria for reporting into the national laboratory surveillance system was obtained during site initiation.

For the quantitative variable person-time at risk, data were censored at the date of a participant's last PCR date up to Jan 11, 2021, with the following cohorts assigned. (1) The cohort susceptible to primary infection: from first antibody-negative date to first positive PCR date or

seroconversion (if no positive PCR test had been reported before seroconversion); or if neither of these occurred, to censor date. (2) The cohort with previous infection: the earliest date for previous infection was taken as whichever was first of the positive PCR result or the onset of COVID-19 typical symptoms (if there was no positive PCR test result), or if neither was available, the first positive antibody test.

The primary outcome was a reinfection in the positive cohort or a primary infection in the negative cohort, determined by PCR tests. No secondary outcomes were analysed.

Statistical analysis

Recruitment continued until March 31, 2021, and more than 44 000 participants were recruited. The study was originally powered to detect a difference in the rate of infection between cohorts with a sample size of 10 000 (25% estimated to be antibody positive at baseline), cumulative incidence of 2%, and immune efficacy of at least 50%.[33] The interim analysis was done as the cumulative incidence in the total cohort reached 7%.

The cohort was described by their baseline cohort allocation. Participants with positive PCR results during follow-up in both negative and positive cohorts were described in more detail. Cumulative incidence (using the total number of participants in each cohort) and incidence density (using the total person-time at risk) were calculated for both cohorts and subcategories and plotted over time using PCR confirmation only.

A proportional hazards frailty model using a Poisson distribution was used to estimate incidence rate ratios (IRRs) to compare the incidence rates in the positive and negative cohorts to provide a relative estimate of the protective effect of a previous SARS-CoV-2 infection. The entry date used in this analysis for all participants was their earliest antibody test. Because the rate of infection in the UK population changed over follow-up time we grouped follow-up time and events by 11 intervals of calendar time. These time intervals were from June 18 to Aug 24, 2020, every 2 weeks between Aug 25 and Dec 28, and then from Dec 29 to Jan 11, 2021. Calendar time was further split into periods when 21 days or more had passed after participants' first vaccine, and when the B.1.1.7 variant became predominant within the region within which they reside. The models were fitted by Poisson regression with a log link, using COVID-19 infection as response, log of exposure times as an offset, and binary indicators for the calendar time intervals as explanatory variables to allow for different piecewise constant hazards.[35] The model fitting approach also provided estimates of the baseline IRRs. The hospital site was added into models as a random effect to account for the extra variation and associated correlation that was not explained by risk and covariate variables. The fixed covariates included in the model were age, gender, ethnicity, region, staff group, and index of multiple deprivation. Time varying covariates included in the model were 21 days after COVID-19 vaccination and regional prevalence of the B.1.1.7 variant. We ran five separate models using the following outcomes: probable reinfections versus all primary infections, infections (reinfection and primary infections) with COVID-19 symptoms, infections with other symptoms, asymptomatic infections, and all infections.

In addition to the aforementioned models, we did a mixed-effects logistic regression analysis as a sensitivity analysis to estimate odd ratios (ORs) to measure the association between the exposure (cohort allocation) and the binary outcome (PCR test result). The entry date used in this analysis for all participants was the earliest antibody test. All PCR tests after the entry date have been used, except PCR tests within 21 days of a positive PCR result. Those in the negative cohort moved to the positive cohort 21 days following a PCR positive test result or at the time of antibody seroconversion with no positive PCR test. To account for temporal changes in the background risk of infection, all tests were allocated to the calendar time groups as previously described. Study site was fitted as a random effect to account for clustering within longitudinal observations, with age group, gender, ethnicity, staff group, index of multiple deprivation, and region fitted as fixed effects, and COVID-19 and regional prevalence of B.1.1.7 fitted as time varying covariates to account for their possible confounding effect.[36] We investigated the association between protection and SGTF, introducing an interaction term into the model; however, the interaction term was not found to be strongly associated and, therefore, was not included in the final model.

All participants meeting the inclusion criteria were included in the analysis, regardless of their testing frequency, with data censored accordingly. The category "unknown" was introduced for variables with missing values, such as symptom status or index of multiple deprivation.

Analyses were done with STATA version 15.1. The trial was registered with ISRCTN, ISRCTN11041050.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 18, 2020, to Dec 31, 2020, 30 625 participants were enrolled into the study. 51 participants withdrew from the study, and then 4913 participants were excluded. A total of 25 661 participants, with linked data on antibody and PCR testing, were included in this analysis (figure 1). Data were extracted from all sources on Feb 5, 2021, and include data up to and including Jan 11, 2021.

The baseline cohorts assigned 8278 (32·3%) of 25 661 participants to the positive cohort and 17 383 (67·7%) to the negative cohort. 7551 (91·2%) of

the 8278 participants in the positive cohort were antibody positive at enrolment, 582 (7·0%) were antibody negative at enrolment but had a previous antibody positive result or positive PCR result (of which 108 also had a previous positive PCR result), and 145 (1·8%) had a previous PCR positive result but no linked antibody data.

Demographics of the SIREN participants by baseline cohort assignment are presented in table 1, and demographics of the positive cohort subdivided by cohort entry requirements are presented in appendix 1 (pp 3–4). In summary, the cohort was predominately female (n=21 617, 84·2%; men, n=4010, 15·6%) and White (n=22 404, 87·3%), with median age 45·7 years (IQR 35·4–53·5), and from clinical occupations with representation from all English regions and about two-thirds of acute hospital trusts. The total follow-up time up to Jan 11, 2021, was 2 047 113 person-days for the positive cohort and 2 971 436 person-days for the negative cohort. The median length of follow-up per participant was 275 days (IQR 218–291) for the positive cohort and 195 days (131–214) for the negative cohort.

The cohort had 220 484 PCR tests (23 321 before SIREN enrolment and 197 163 after enrolment) and 135 890 antibody tests (16 862 before SIREN enrolment and 119 028 after enrolment). A median of eight post-enrolment PCR tests (IQR 6–11) and five post-enrolment antibody tests (3–7) were done. The PCR test density during follow-up was 64 per 1000 days of participant follow-up in the positive cohort and 70 per 1000 days of participant follow-up in the negative cohort.

13 401 (52·2%) participants of the cohort were vaccinated during the follow-up period (between Dec 8, 2020, and Jan 11, 2021), 9468 in the negative cohort and 3933 in the positive cohort. Vaccine roll-out accelerated in January, 2021, and peaked during the week commencing Jan 11, 2021. The number of participants who contributed follow-up time to this analysis who had been vaccinated for 21 days or more, the period at which a protective effect from vaccination would be expected, was 833 from the positive cohort, contributing 4941 days of follow-up, and 2279 from the negative cohort, contributing 12 839 days of follow-up. In total 0·4% of the study's person-time of follow-up included participants 21 days or more following vaccination.

The weekly total of new PCR positive tests (primary infection) and reinfections in SIREN participants between March, 2020, and January, 2021, by baseline cohort assignment are presented in figure 2. PCR positivity for primary infections in the positive cohort peaked in the first week of April whereas in the negative cohort PCR positivity peaked in the last week of December, 2020. The weekly frequency of reinfections has been much lower and more constant, peaking in the last week of December at 22 reinfections.

By Jan 11, 2021, 1859 new infections were detected in the study population: 1704 primary infections in the negative

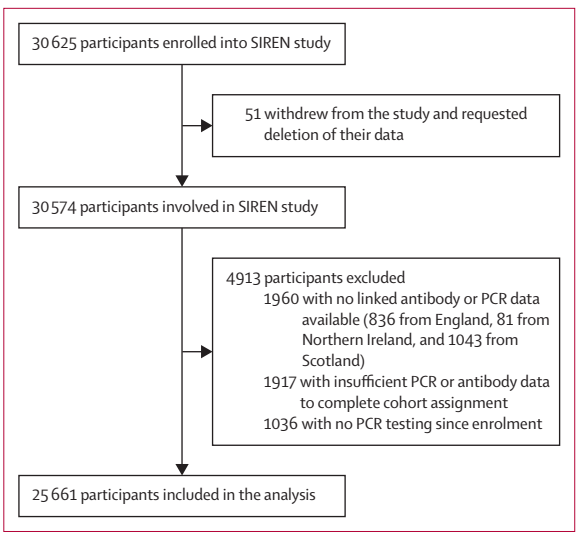

Figure 1: **Study profile**
Participants were enrolled June 18–Dec 31, 2020. SIREN=The SARS-CoV-2 Immunity and Reinfection Evaluation study.

	Positive cohort (n=8278)	Negative cohort (n=17 383)	All participants (n=25 661)
Gender			
Female	6840 (82·6%)	14 777 (85·0%)	21 617 (84·2%)
Male	1425 (17·2%)	2585 (14·9%)	4010 (15·6%)
Other	13 (0·2%)	21 (0·1%)	34 (0·1%)
Age, years			
Median (IQR)	45·6 (34·6–53·8)	45·7 (35·8–53·9)	45·7 (35·4–53·5)
Range	18·6–78·4	18·6–84·3	18·6–84·3
Ethnicity			
White	6969 (84·2%)	15 435 (88·8%)	22 404 (87·3%)
Mixed race	724 (8·7%)	1049 (6·0%)	1773 (6·9%)
Asian	236 (2·9%)	289 (1·7%)	525 (2·0%)
Black	134 (1·6%)	278 (1·6%)	412 (1·6%)
Chinese	147 (1·8%)	199 (1·1%)	346 (1·3%)
Other ethnic group	51 (0·6%)	100 (0·6%)	151 (0·6%)
Prefer not to say	17 (0·2%)	33 (0·2%)	50 (0·2%)
Medical conditions			
No medical condition	6195 (74·8%)	12 930 (74·4%)	19 125 (74·5%)
Chronic respiratory conditions	1019 (12·3%)	2229 (12·8%)	3248 (12·7%)
Chronic non-respiratory conditions	909 (11·0%)	1837 (10·6%)	2746 (10·7%)
Immunosuppression	155 (1·9%)	387 (2·2%)	542 (2·1%)
Staff group			
Nursing or health-care assistant	3751 (45·3%)	7140 (41·1%)	10 891 (42·4%)
Administrative or executive	1090 (13·2%)	2813 (16·2%)	3903 (15·2%)
Doctor	999 (12·1%)	1784 (10·3%)	2783 (10·8%)
Specialist staff	489 (5·9%)	1059 (6·1%)	1548 (6·0%)
Health-care scientist	225 (2·7%)	669 (3·8%)	894 (3·5%)
Midwife	189 (2·3%)	460 (2·6%)	649 (2·5%)
Pharmacist	112 (1·4%)	278 (1·6%)	390 (1·5%)
Estates, porters, or security	95 (1·1%)	161 (0·9%)	256 (1·0%)
Other	1328 (16·0%)	3019 (17·4%)	4347 (16·9%)

(Table 1 continues on next page)

	Positive cohort (n=8278)	Negative cohort (n=17 383)	All participants (n=25 661)
(Continued from previous page)			
Patient-facing role			
Yes	7280 (87·9%)	14 832 (85·3%)	22 112 (86·2%)
No	998 (12·1%)	2551 (14·7%)	3549 (13·8%)
Index of multiple deprivation*			
1	1054 (12·7%)	1862 (10·7%)	2916 (11·4%)
2	1469 (17·7%)	3094 (17·8%)	4563 (17·8%)
3	1823 (22·0%)	4019 (23·1%)	5842 (22·8%)
4	1880 (22·7%)	4125 (23·7%)	6005 (23·4%)
5	1968 (23·8%)	4127 (23·7%)	6095 (23·8%)
Unknown	84 (1·0%)	156 (0·9%)	240 (0·9%)
Region			
South West	1155 (14·0%)	4155 (23·9%)	5310 (20·7%)
London	1273 (15·4%)	1918 (11·0%)	3191 (12·4%)
North West	1229 (14·8%)	1888 (10·9%)	3117 (12·1%)
East of England	863 (10·4%)	2086 (12·0%)	2949 (11·5%)
South East	914 (11·0%)	1996 (11·5%)	2910 (11·3%)
East Midlands	878 (10·6%)	1800 (10·4%)	2678 (10·4%)
West Midlands	833 (10·1%)	1779 (10·2%)	2612 (10·2%)
Yorkshire and the Humber	926 (11·2%)	1394 (8·0%)	2320 (9·0%)
North East	207 (2·5%)	367 (2·1%)	574 (2·2%)

Data are n (%), unless otherwise indicated. *1 indicates most deprived and 5 indicates least deprived. Participants were enrolled from June 18 to Dec 31, 2020.

Table 1: **Demographics of study participants by baseline cohort allocation**

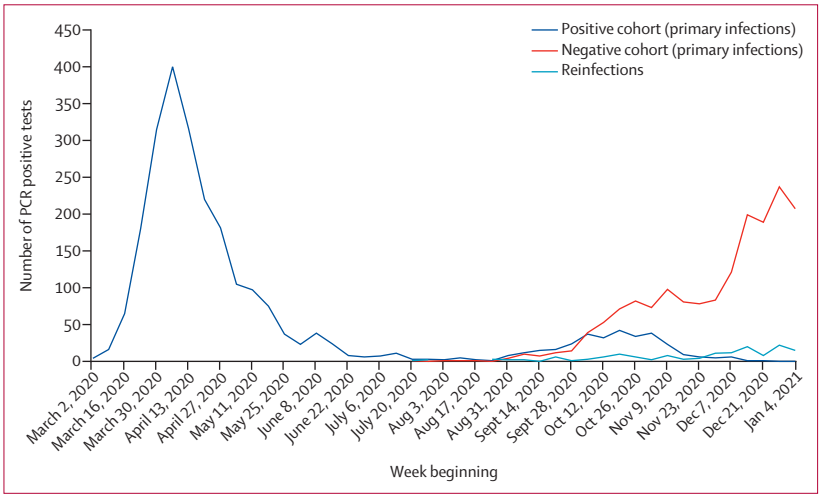

Figure 2: **Weekly frequency of SIREN participants with a first positive PCR test result by baseline cohort assignment, from March, 2020, to January, 2021**
SIREN=The SARS-CoV-2 Immunity and Reinfection Evaluation study.

See Online for appendix 2

cohort and 155 reinfections in the positive cohort (table 2). Of the primary infections, 1369 (80·3%) of these cases were symptomatic at infection, 1126 (66·1%) with typical COVID-19 symptoms, and 243 (14·3%) with other symptoms; 293 (17·2%) were asymptomatic; and 42 (2·5%) did not complete a questionnaire at the time of their symptoms. There were 864 seroconversions in participants without a positive PCR test; these were not included as primary infections in this interim analysis.

155 reinfections were identified in the positive cohort, two of which were categorised as probable and 153 as possible (table 2). 78 reinfections (50·3%) were symptomatic, 50 (32·3%) with typical COVID-19 symptoms, including both probable cases. At baseline antibody testing 127 of the reinfection cases were antibody positive, 18 were antibody negative but had a previous antibody positive or positive PCR test result, seven had no history of an antibody positive result but had a previous positive PCR result, and three participants who were antibody negative at baseline had moved cohort, having had both a primary infection and reinfection, during follow-up.

The median interval between the primary infection and reinfection episode for the 47 cases with a positive PCR test from their primary episode was 201 days (range 95–297; table 2). For the 99 cases who provided a history of COVID-19 symptoms, used as a proxy to estimate the date of their primary infection, the median interval between primary infection and reinfection was 241 days (range 90–345).

Between June, 2020, and January, 2021, the cumulative incidence of probable symptoms was 0·2 cases per 1000 participants, with 6·0 cases per 1000 for COVID-19 symptoms, 3·4 cases per 1000 for other symptoms, 9·2 cases per 1000 for asymptomatic cases, and 18·7 cases per 1000 for all reinfections in the positive cohort. The incidence of COVID-19 symptomatic infections was 64·8 cases per 1000 participants, other symptomatic infections was 14·0 cases per 1000, asymptomatic cases was 16·9 cases per 1000, and all new PCR positive infections was 98·0 cases per 1000 in the negative cohort (table 3). The incidence density between June, 2020, and January, 2021, was 7·6 reinfections per 100 000 person-days of follow-up in the positive cohort and 57·3 new PCR positive infections per 100 000 person-days of follow-up in the negative cohort.

The results of our proportional hazards model are presented in table 4, with more detailed outputs on the covariates presented in appendix 1 (pp 5–9). The mixed-effects logistic regression model produced consistent results, which are presented in appendix 2. Restricting reinfections to probable reinfections only, we estimated that between June, 2020, and January, 2021, after controlling for other risk factors and for a given site, participants in the positive cohort had 99·8% lower risk of new infection than did participants in the negative cohort, adjusted IRR (aIRR) 0·002 (95% CI 0·00–0·01). Restricting infections to those who had COVID-19 symptoms, we estimated that participants in the positive cohort had a 93% lower incidence of new infection than did participants in the negative cohort, aIRR 0·074 (95% CI 0·06–0·10). Using our most sensitive definition of reinfections, including all those who were possible or probable, the aIRR was 0·159 (95% CI 0·13–0·19). Although our results

	Positive cohort			Negative cohort
	Probable (n=2)	Symptomatic (n=78)	All reinfections (n=155)	New positive PCR cases (n=1704)
Gender				
Female	2 (100·0%)	63 (80·8%)	124 (80·0%)	1439 (84·4%)
Male	0	14 (17·9%)	30 (19·4%)	262 (15·4%)
Other	0	1 (1·3%)	1 (0·6%)	3 (0·2%)
Age, years				
Median (range)	41·5 (37–46)	42·4 (20–64)	46·7 (20–68)	43·2 (19–71)
Antibody status at baseline				
Antibody positive	2 (100·0%)	56 (71·8%)	127 (81·9%)	0
Previous positive PCR test and no antibody data	0	1 (1·3%)	2 (1·3%)	0
Antibody negative, previously antibody positive and positive PCR test	0	4 (5·1%)	5 (3·2%)	0
Antibody negative and previously antibody positive	0	11 (14·1%)	13 (8·4%)	0
Antibody negative with previous positive PCR test	0	3 (3·8%)	5 (3·2%)	0
Antibody negative, not previously antibody positive, no previous positive PCR test*	0	3 (3·8%)	3 (1·9%)	1704 (100·0%)
Reinfection PCR semi-quantitative values (Ct/RLU)				
Ct (range)	22·3 (21–24)	26·9 (13–37)	28·0 (13–45)	..
Number of participants	2	26	49	..
RLU (range)	..	1188·0 (587–1315)	1101·0 (576–2203)	..
Number of participants	..	17	49	..
Symptom status 14 days before or after positive PCR test				
COVID-19 symptoms	2 (100·0%)	50 (64·1%)	50 (32·3%)	1126 (66·1%)
Other symptoms	0	28 (35·9%)	28 (18·1%)	243 (14·3%)
No symptoms	0	0	76 (49·0%)	293 (17·2%)
Unknown	0	0	1 (0·6%)	42 (2·5%)
Time between primary infection and reinfection, days				
Symptom onset first episode to reinfection PCR test	212 (197–227)	261·5 (90–345)	241 (90–345)	..
Number of participants	2	46	99	..
First positive PCR test to reinfection PCR test	..	215 (95–297)	201 (95–297)	..
Number of participants	..	22	47	..
First antibody positive result to reinfection PCR test	63 (62–64)	148 (29–215)	135 (29–218)	..
Number of participants	2	69	141	..

Data are n, n (%), or median (range), unless otherwise indicated. SIREN=The SARS-CoV-2 Immunity and Reinfection Evaluation study. Ct=cycle threshold. RLU=relative light unit. *Three participants had both a primary infection and a reinfection during SIREN follow-up and are in both columns, but were antibody negative at enrolment.

Table 2: **Characteristics of reinfections and new infections detected in SIREN participants up to Jan 11, 2021, stratified by case definition**

showed that previous infection offered protection against all five categories of reinfection, the lowest protection was provided to asymptomatic infection (aIRR 0·48 95% CI 0·37–0·63).

We did not find any evidence that increased prevalence of the B.1.1.7 variant adversely affected reinfection rates in our cohort during this follow-up period. Our models suggested that the protective effect of previous infection increased when the variant was dominant (IRR 0·18, 95% CI 0·15–0·23) compared with IRR 0·13 (0·10–0·17), although the formal test of interaction between cohort and SGTF did not reach conventional levels of statistical significance (p=0·05). Additionally, the ecological nature of the SGTF data available to use precludes the ability to definitively answer the question of protection conferred to new variants.

Discussion

We have presented the interim findings after 7 months of follow-up from the SIREN study, a unique, large-scale, multicentre, prospective cohort study of health-care staff undergoing frequent asymptomatic testing, powered to detect and characterise reinfections and estimate the protective effect of SARS-CoV-2 antibodies.

We have detected two probable reinfections and 153 possible reinfections in our positive cohort. 50 of the reinfections were symptomatic with typical COVID-19 symptoms, 28 with other symptoms, and 76 were asymptomatic. By contrast, we identified 1704 new PCR positive infections in patients, 1126 of whom had COVID-19 symptoms, 243 with other symptoms, and 293 were asymptomatic in our negative cohort. Using a COVID-19 symptomatic case definition aligned with

	Positive cohort (n=8278)*			Negative cohort (n=17 383)†		
	n	Incidence of reinfections		n	Incidence of new infections	
		Cumulative (cases per 1000 participants)	Density (reinfections per 100 000 days)		Cumulative (cases per 1000 participants)	Density (new infections per 100 000 days)
Probable	2	0·2	0·1	..	..	..
COVID-19 symptoms‡	50	6·0	2·4	1126	64·8	37·9
Other symptoms§	28	3·4	1·4	243	14·0	8·2
Asymptomatic	76	9·2	3·7	293	16·9	9·9
All events	155	18·7	7·6	1704	98·0	57·3

*Person-time at risk was 2 047 113 days. †Person-time at risk was 2 971 436 days. ‡COVID-19 symptoms included any of cough, fever, anosmia, or dysgeusia. §Other symptoms include any of sore throat, runny nose, headache, muscle aches, fatigue, diarrhoea, vomiting, or itchy red patches.

Table 3: **Frequency of new infections and reinfections by cohort, characterised by case definitions and symptoms 14 days before and after date of positive PCR test**

	n	IRR (95% CI)	p value	aIRR (95% CI)	p value
Probable	2	0·002 (0·00–0·01)	<0·0001	0·002 (0·00–0·01)	<0·0001
COVID-19 symptoms	50	0·079 (0·06–0·11)	<0·0001	0·074 (0·06–0·10)	<0·0001
Other symptoms	28	0·219 (0·15–0·33)	<0·0001	0·215 (0·14–0·32)	<0·0001
Asymptomatic	76	0·503 (0·39–0·65)	<0·0001	0·484 (0·37–0·63)	<0·0001
All events	155	0·169 (0·14–0·20)	<0·0001	0·159 (0·13–0·19)	<0·0001

IRR unadjusted model was adjusted for period and site. IRR adjusted model included fixed effects (adjusted for week group, age group, gender, ethnicity, staff role, index of multiple deprivation, region); time-varying effects (adjusted for vaccination and B.1.1.7 variant prevalence); and random effect (adjusted for site). SIREN=The SARS-CoV-2 Immunity and Reinfection Evaluation study. IRR=incidence rate ratio. aIRR=adjusted incidence rate ratio. *Both probable cases had COVID-19 symptoms and one reinfection case did not provide details on symptoms so the results for this participant are unknown.

Table 4: **Univariable and multivariable analysis of risk of infection by cohort during SIREN follow-up, using a range of reinfection case definitions, between June 18 and Jan 11, 2021***

positive PCR results, previous infection reduced the incidence of infection by at least 90% (aIRR 0·07, 95% CI 0·06 to 0·10) and even when we included all possible and probable reinfections reduced the incidence of reinfection by at least 84% (aIRR 0·159, 0·13–0·19).

We believe this is the minimum probable effect because the curve in the positive cohort was gradual throughout, indicating some of these potential reinfections were probably residual RNA detection at low population prevalence rather than true reinfections. In the negative cohort, the gradient was shallow up to late September, 2020, and then accelerated, increasing again from late November, 2020, coinciding with the period when community prevalence increased rapidly.[37] Additionally, we did not include 864 seroconversions in the negative cohort, because these seroconversions were not detected by PCR and whether a similar rate of undetected infections occurred in the positive cohort remains unknown.

None of the reinfections we have identified are confirmed by our stringent case definitions, most reinfections we only consider possible and are undergoing further serological investigation. Investigations have been restricted by the scarce data and samples from historic infections, with most swabs discarded without sequencing, preventing the genomic comparison between infection episodes required to confirm a reinfection. This finding emphasises the importance of SIREN, through which we are ensuring the data collection and characterisation of new infections, to build a stronger base to investigate and confirm future reinfections. Our use of hierarchical case definitions identifies cases with stronger evidence and allows us to present the range of potential reinfection scenarios.

Another limitation is measurement error when capturing the primary infection onset date for positive cohort participants without a positive PCR test associated with their primary episode. This limitation introduces imprecision into our person-time at risk, and consequently reinfection rates, and our estimated intervals between primary infection episodes and reinfections. For those who were symptomatic in their primary episode we have used their self-reported COVID-19 symptom onset date as a proxy, which could be subject to recall bias. However, we have introduced validation rules to reduce the recall bias, excluding onset dates before March, 2020. We used the first antibody positive date for participants with asymptomatic or non-COVID-19 symptomatic primary infections. Therefore, we did not capture the entire time period during which participants were susceptible to reinfection, reducing our overall follow-up time for this cohort, and thus inflating our reinfection rates and reducing our intervals between infection episodes.

Because the cohort assignment was determined by testing at SIREN sites, which use a range of testing platforms and assays, misclassification bias might have occurred. We have included participants in the positive cohort who had a previous positive PCR test, irrespective of their antibody status, although these participants account for less than 4% of the positive cohort. Some of those PCR results, especially early in the epidemic, might have been false positives or laboratory contamination episodes, particularly when considering that cycle threshold/relative light unit values are not available. We aim to retest all baseline serum samples within Public

Health England, using both S and N target assays to give each participant a validated quantitative baseline antibody result. This testing will inform future analyses and might lead to changes to the cohort assignment presented.

Although COVID-19 vaccines were introduced to our cohort from Dec 8, 2020, onwards, the effect on the follow-up time in this analysis was modest and has been adjusted for, therefore our finding on the durability of protection following previous infection is independent of the vaccine effect. However, we note that given the high vaccination coverage in the SIREN cohort, future analyses will need to estimate both the protective effect of previous infections and vaccine effectiveness simultaneously.

Finally, this interval analysis covers the period of the emergence and spread of the B.1.1.7 lineage (VOC202012/01) with multiple non-synonymous spike mutations including N501Y; a variant of concern due to its increased transmissibility and, potentially, increased disease severity.[34,38,39] Previous studies have shown that commercially available vaccines in the UK are still effective against this new variant, inducing a neutralising antibody response and offering similar protection when compared with other lineages.[40–42] We have shown in this analysis that immunity from previous infection is protective against reinfection with the B.1.1.7 variant.

Our results are consistent with the findings from other smaller studies of decreased incidence of PCR positivity in antibody-positive individuals.[30,32] Another prospective cohort of health-care workers previously reported the incidence of new positive PCR-confirmed infections to be lower among seropositive than seronegative participants (three of 1246 *vs* 165 of 11 052, an incidence density of 2·1 per 100 000 days at risk for seropositive participants and 8·6 per 100 000 days at risk for seronegative participants).[30] However, this study did not routinely do PCR tests on all individuals in the cohort and the three potential reinfections were asymptomatic.

The SARS-CoV-2 vaccination trials have typically investigated protection from symptomatic infection. The ChAdOx1 trial reported protection against symptomatic infection (COVID-19 typical symptoms) of between 62·1% and 90% over 2 months of follow-up, and the BNT162b2 vaccine phase 3 results reported 95% protection over 3 months of follow-up.[28,29] Another phase 3 trial of the mRNA-1273 vaccine showed 94·1% efficacy against symptomatic (COVID-19 typical symptoms) SARS-CoV-2 infection, including severe illness, over a median of 2 months of follow-up.[43] In a separate analysis on the SIREN cohort, we showed that the BNT162b2 vaccine offered 70% protection from both symptomatic and asymptomatic infection, 21 days after the first dose, which increased to 85% 7 days after the second dose.[44] Our findings of a 93% lower risk of COVID-19 symptomatic infection, after a longer period of follow-up, show equal or higher protection from natural infection, both for symptomatic and asymptomatic infection.

After 7 months of follow-up, this large observational study showed that previous SARS-CoV-2 infection protects most individuals against reinfection for an average of 7 months. We have identified and investigated more potential reinfections than reported in the global literature to date, supporting the value of large prospective cohort studies such as SIREN. This study supports the hypothesis that primary infection with SARS-CoV-2 provides a high degree of immunity to repeat infection in the short to medium term; with similar levels of prevention of symptomatic infection as the new licenced vaccines for working-age adults. We have also shown that immunity from previous infection is protective against reinfection with the B.1.1.7 variant. Primary infection also reduces the risk of asymptomatic infection and thus onward transmission; this is particularly important as health care was considered a potential driver for ongoing community transmission during the first wave in the UK.[45] Our findings increase the likelihood that this protection could also be attainable by vaccine-induced immunity, which a separate analysis on the SIREN cohort previously demonstrated.[44] Further detailed studies on the longevity of antibody responses, assessment of reinfection rates under the challenge of the new lineages, and the effect of all COVID-19 vaccines introduced in the UK are underway in this cohort.

Contributors

VJH, SF, and SH designed the analysis plan and wrote the paper. SF and VJH cleaned and finalised the dataset for analysis and did the descriptive analyses. AC and AS planned and did the statistical analysis. RS, EW, PDK, SF, KM, and AV set up and ran the data collection systems and linkage of participant records. AV, MK, PDK, VJH, and SH designed, piloted, and built the online questionnaires. MAC, CSB, SH, TB, MZ, MJC, AA, EJMM, SR, BO, SW, MS, VJH, MR, and RS designed the reinfection investigation pathways and investigated reinfections. AA, EJMM, BO, SW, MS, SR, and MJC led onsite recruitment and initiation. VJH, SF, AC, AS, and AA verified the data in the study. All authors reviewed and approved the manuscript for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

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

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