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Research paper

Prevalence of antibody positivity to SARS-CoV-2 following the first peak of infection in England: Serial cross-sectional studies of 365,000 adults

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ABSTRACT

Background: The time-concentrated nature of the first wave of the COVID-19 epidemic in England in March and April 2020 provides a natural experiment to measure changes in antibody positivity at the population level before onset of the second wave and initiation of the vaccination programme.
Methods: Three cross-sectional national surveys with non-overlapping random samples of the population in England undertaken between late June and September 2020 (REACT-2 study). 365,104 adults completed questionnaires and self-administered lateral flow immunoassay (LFIA) tests for IgG against SARS-CoV-2.
Findings: Overall, 17,576 people had detectable antibodies, a prevalence of 4.9% (95% confidence intervals 4.9, 5.0) when adjusted for test characteristics and weighted to the adult population of England. The prevalence declined from 6.0% (5.8, 6.1), to 4.8% (4.7, 5.0) and 4.4% (4.3, 4.5), over the three rounds of the study a difference of -26.5% (-29.0, -23.8). The highest prevalence and smallest overall decline in positivity was in the youngest age group (18-24 years) at -14.9% (-21.6, -8.1), and lowest prevalence and largest decline in the oldest group (>74 years) at -39.0% (-50.8, -27.2). The decline from June to September 2020 was largest in those who did not report a history of COVID-19 at -64.0% (-75.6, -52.3), compared to -22.3% (-27.0, -17.7) in those with SARS-CoV-2 infection confirmed on PCR.
Interpretation: A large proportion of the population remained susceptible to SARS-CoV-2 infection in England based on naturally acquired immunity from the first wave. Widespread vaccination is needed to confer immunity and control the epidemic at population level.
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1. Introduction

Representative national prevalence surveys of SARS-CoV-2 antibodies provide insights into sociodemographic variation and extent of infection in the population and increase understanding of the future course of the epidemic [1]. Studies in Iceland [2] and Spain [3] found differing levels of population antibody positivity, with evidence in Iceland of durable antibody response over 4 months. Emerging evidence from follow-up studies suggest that many individuals may have durable immune responses following symptomatic infection but that, in some, antibody levels fall with time after infection, influenced by factors including the severity of initial illness, age and co-morbidities [4–7].

Changes in population antibody prevalence over time will reflect the combination of incidence of new infections, uptake of vaccination

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Research in context

Evidence before this study

The proportion of individuals in a population with evidence of protective immunity against SARSCoV2 is an important determinant for ongoing transmission. Cross-sectional estimates of prevalence will be affected by previous infection and vaccination, but also the rate of loss of antibody following infection. In cohort studies of symptomatic individuals, there is evidence that antibody responses can remain high for at least six months after infection and national seroprevalence studies such as those in Iceland and Spain have given robust cross-sectional estimates of population antibody positivity. However, to date there have been no longitudinal population studies to monitor changes in prevalence of antibody responses over time including in people with mild or no symptoms.

Added value of this study

The first peak of SARS-CoV-2 infection in England was concentrated between March and April 2020, followed by a five-month period of low transmission. This provided a unique opportunity for detailed exploration of factors associated with antibody positivity and longitudinal study of the population prevalence of anti-SARS-CoV-2 IgG antibody positivity. This study is the first to demonstrate a decline in population prevalence of detectable IgG antibodies following a peak in SARS-CoV-2 infection, with a fall of 25.6% over three months. The largest decline was seen in individuals aged 75 or older and those who did not report a history of symptomatic infection.

Implications of all the available evidence

Longitudinal studies of immune responses to SARS-CoV-2 in symptomatic individuals are not representative of the infected population as a whole, approximately 1/3 of whom have asymptomatic or mild infection. The largest study of its kind, this study demonstrates a significant decline in population antibody positivity over 3 months, with higher rates of decline in those without symptomatic infection. Such trends need to be accounted for in future cross-sectional surveys of previous infection. In the absence of access to vaccination, waning antibody positivity is likely to be associated to an increased susceptibility to reinfection, as is the case with other endemic seasonal coronaviruses.

and waning of detectable antibody levels in those previously infected. Sequential prevalence surveys can help quantify the durability of antibody responses, key to understanding how population immunity may prevent reinfection and limit further transmission.

In England, the widespread outbreak of COVID-19 in March and April 2020 led to high associated mortality [8]. A national lockdown with the closure of schools, universities, hospitality, all but essential retail, and advice to work from home and avoid non-essential travel, was introduced in late March with a marked reduction in new infections until late August 2020 [9].

The large and rapid initial peak of infection in England provides a unique natural experiment with which to understand the progression of natural immunity in the population. We previously reported antibody positivity based on a self-administered lateral flow immunoassay (LFIA) test from a representative survey of 105,000 individuals during June and July 2020 [10]. We report here the levels and changing prevalence of detectable antibody across this and two further cross-sectional national surveys through September 2020 as part of the REal-time Assessment of Community Transmission-2 (REACT-2) programme and the association with social, demographic and clinical features.

2. Methods

The REACT study protocol has been published [11]. Briefly, we included non-overlapping community samples from the adult population 18 years and older, using a self-administered questionnaire and LFIA test at home (Table 1) [10,11]. Invitations were sent to named individuals randomly selected from the National Health Service (NHS) patient list which includes anyone registered with a General Practitioner (primary care physician) in England, covering almost the entire population. We aimed for a sample size of 100,000 in rounds 1 and 2 and 150,000 in round 3 to obtain prevalence estimates for the 315 lower tier local authorities in England. A lower tier local authority (LTLA) is an administrative unit within England which variably consists of local authority districts, unitary authorities, metropolitan districts and London boroughs. Sample size calculations [11] and the number of invitations sent out was based on an assumed response rate of 36% to 38% based on previous surveys. Registration was closed after 125,000 people signed up in rounds 1 and 2, and after 195,000 in round 3. Across all three rounds, 37.7% of those invited registered, and 29.9% provided a valid (IgG positive or negative) antibody result (Supplementary Table S1). The response rate declined slightly over the three rounds although the balance of respondents by sex, age, region, ethnicity and deprivation was similar (Supplementary Table S2). Those who registered were posted a self-administered point-of-care LFIA test (Fortress Diagnostics, Northern Ireland) with written and video instructions. The assay uses the S1 subunit (including RBD). The sensitivity of finger-prick blood (self-read) for IgG antibodies was 84.4% (70.5, 93.5) in RT-PCR confirmed cases in healthcare workers, and specificity 98.6% (97.1, 99.4) in pre-pandemic sera [12]. Participants completed a short registration questionnaire (online/telephone) and a further survey upon completion of their self-test. Survey instruments are available on the study website (https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/).

Table 1
Prevalence[1] of antibody positivity to SARS-CoV-2 using LFIA test over three study rounds from June to September 2020.

	IgG antibody positive	Total tests (with valid results)	Crude prevalence % [95% CI]	Adjusted & weighted[1] prevalence % [95% CI]
Round 1 (20 Jun - 13 July)	5544	99908	5.55 [5.41-5.69]	5.96 [5.78-6.14]
Round 2 (31 Jul – 13 Aug)	4995	105829	4.72 [4.59-4.85]	4.83 [4.67-5.00]
Round 3 (15 - 28 Sept)	7037	159367	4.42 [4.32-4.52]	4.38 [4.25-4.51]
All rounds	17576	365104	4.81 [4.75-4.88]	4.94 [4.85-5.03]

LFIA = lateral flow immunoassay.
[1] Prevalence adjusted for test characteristics, weighted to the age, sex, region, ethnicity, index of multiple deprivation of England population (see appendix supplementary methods for detail on weighting).

The prevalence from each round was calculated as the proportion of individuals reporting a valid test result with a positive IgG result, adjusted for test performance, [13] and weighted at national level for age, sex, region, ethnicity and deprivation to the adult population of England (Supplementary Methods). Index of Multiple Deprivation 2019 (IMD) was used as a measure of relative deprivation, based on seven domains at a small local area level across England (income, employment, education, health, crime, barriers to housing and services, and living environment) [14]. The change in prevalence was estimated between successive rounds and from the first to the third round, and reported at national, regional and local geographic area, and by sociodemographic and clinical characteristics. We used complete case analysis without imputation. Confidence intervals for the changes in prevalence were calculated using a normal approximation to the sampling distribution of a difference in prevalences [15].

Epidemic curves were constructed retrospectively using information from participants with a positive antibody test who reported date of onset for a confirmed or possible case of COVID-19, i.e. excluding those who were asymptomatic and for whom date of onset was unknown.

To establish the sensitivity of the Fortress LFIA in relation to titres of neutralising antibodies we established endpoint neutralization titres for 49 sera from healthcare workers at 21 days or more since confirmed RT-PCR diagnosis of SARS-CoV-2 infection, using live virus neutralization tests as previously described [12,16].

Data were analysed using the statistical package R version 4.0.0 [17].

We obtained research ethics approval from the South Central-Berkshire B Research Ethics Committee (IRAS ID: 283805), and Medicines and Healthcare products Regulatory Agency approval for use of the LFIA for research purposes only. A REACT Public Advisory Group provides input into the design and conduct of the research.

3. Role of the Funding Source

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

4. Results

Results were available for 99,908, 105,829 and 159,367 people over the three rounds, which took place approximately 12, 18 and 24 weeks after the peak of the epidemic in England in March and early April. Round 1 was from 20 June to 13 July 2020, Round 2 from 31 July to 13 August 2020, and Round 3 from 15 to 28 September 2020. There were 17,576 positive tests in total. National antibody prevalence, adjusted for test characteristics and weighted to the adult population of England, declined from 6.0% (5.8, 6.1), to 4.8% (4.7, 5.0) and 4.4% (4.3, 4.5), a difference of -26.3% (-29.0, -23.8) over the three rounds (Table 1, Supplementary Table S3). The fall was larger between rounds 1 and 2 at -19.0% (-21.8, -16.1) than between 2 and 3 at -9.1% (-12.0, -6.2).

The epidemic curves constructed from people who tested positive and reported symptoms closely overlap for each of the three rounds, illustrating the relatively short, concentrated outbreak across the country, with a steep decline in new cases from 6 April, two weeks after the national lockdown was announced on 23 March (Fig. 1). Few new cases were reported between May and September 2020.

Over the three rounds of study we found similar patterns of infection to those reported in round 1 during June–July 2020 [10]. Prevalence was highest for ages 18–24 years and lowest in those aged 75 and over. In the third round (September 2020), prevalence was highest in London at 9.5% (9.0, 9.9) – down from 13.0% [12.3, 13.6] in June-July – compared with 1.6% (1.3, 1.9) in the South West of England. People of Black (includes Black Caribbean, African and Black British) and Asian (mainly South Asian) ethnicity had higher prevalence at 13.8% (12.6, 15.1) and 9.7% (9.1, 10.4) respectively, than those of white ethnicity at 3.6% (3.5, 3.8). Prevalence was also higher among people working in healthcare and social (residential) care, those living in more deprived areas and larger households (Supplementary Table S3).

There was a decline in prevalence between June–July and September 2020 in all age groups, with the smallest overall decline for ages 18–24 years at -14.9% (-21.6, -8.1) and largest for ages 75 years and over at -39.0% (-50.8, -27.2) (Fig. 2). The decline was largest in groups who did not report a history of COVID-19 at -64.0% (-75.6, -52.3), compared to -22.3% (-27.0, -17.7) in those groups with COVID-19 confirmed on RT-PCR. There was no change in prevalence over this period in healthcare workers at +3.45% (-5.7, +12.7). There was a decline in prevalence in most local areas over the three rounds (Supplementary Figures S1, S2)

We found a high level of consistency in the sensitivity cut-off points between the Fortress LFIA batches used in round 1 and round 2 (also used in round 3) (Supplementary Figure S3). We employed live virus neutralization assays to understand the limit of sensitivity of the LFIA. Sera from healthcare workers who had recovered from SARS-CoV-2 infection and who scored positive on the LFIA had a median neutralization titre of 1:40 compared with a median below the limit of detection of the assay for those who scored negative (z score 3.68, P=0.0002) (Fig. 3).

5. Discussion

There has been a high burden of infection in England, with over 2.1 million diagnosed infections and 64,118 deaths with COVID-19 on the death certificate recorded within 28 days by the end of 2020. Our data capture a unique moment in the epidemic following the initial high rates of infection during the first wave and then low levels of transmission before the second wave and before introduction of a population vaccination programme. We have shown that at the end of September 2020, over 95% of the population did not have detectable antibodies on the self-administered LFIA test, indicating that a large proportion of the population remained susceptible to infection. In addition, we detected a 26% reduction in antibody positivity over the four months between the first and third rounds of the study, which took place 3 and 6 months after the first wave of infections respectively. This is consistent with evidence that immunity to seasonal coronaviruses declines over 6 to 12 months after infection, and emerging data on SARS-CoV-2 that indicate a decrease over time in antibody levels in a proportion of individuals followed in longitudinal studies, although other studies indicate persistence for at least six months [4,18–20]. We observed differences in rates of decline between groups, for example those reporting SARS-CoV-2 infection based on RT-PCR versus those without a history of COVID-19. In some groups with continued exposure risks, no change in prevalence was seen (e.g. healthcare workers) and the lower decline among younger age groups could reflect some incident cases in between rounds, although the overall number of new cases was small during these months.

During any antibody response to an acute pathogen, some level of antibody waning in the months following infection is expected as short-lived plasmablasts die. Low levels of affinity-matured antibodies usually continue to be produced by long-lived plasmacells and may be sufficient to maintain levels of antibody that confer immunity. Indeed, for some pathogens such as measles, influenza and rhinovirus, antibodies can be detected for many years after infection. However, the situation for coronaviruses (and SARS-CoV-2 in particular) is less clear. Human challenge studies show a more profound waning of serum and nasal antibody over one year following seasonal coronavirus challenge than seen for volunteers challenged with rhinovirus.

The relevance of antibody waning for the potential for reinfection by SARS CoV-2 is currently unresolved [21]. Descriptions of the decline following infection are variable, with a general consensus that IgG levels can remain high for at least 2-3 months before declining, [19,22] but those with smaller initial antibody responses are likely to decline earlier [19]. Decline may initially be rapid, before plateauing, but data on this are only now beginning to emerge.

Moreover modelling shows that waning immunity can explain the 1−2 year periodicity of reinfections with seasonal coronaviruses [23]. Although reports of reinfection with SARS-CoV-2 have been limited to date, [24] this is in part because definitive evidence of reinfection requires sequencing of virus at two time points, which is rarely available in practice. In addition, asymptomatic testing is not yet widespread in many countries and thus mild or asymptomatic reinfections may go undetected.

It is widely thought that titres of anti-Spike (S) antibodies which target the receptor binding domain (RBD, associated with cell entry) correlate with protection from reinfection [25]. In individuals with strong neutralising antibody titres, these may be maintained for at least 6 months [20]. The LFIA used for this study detects antibodies

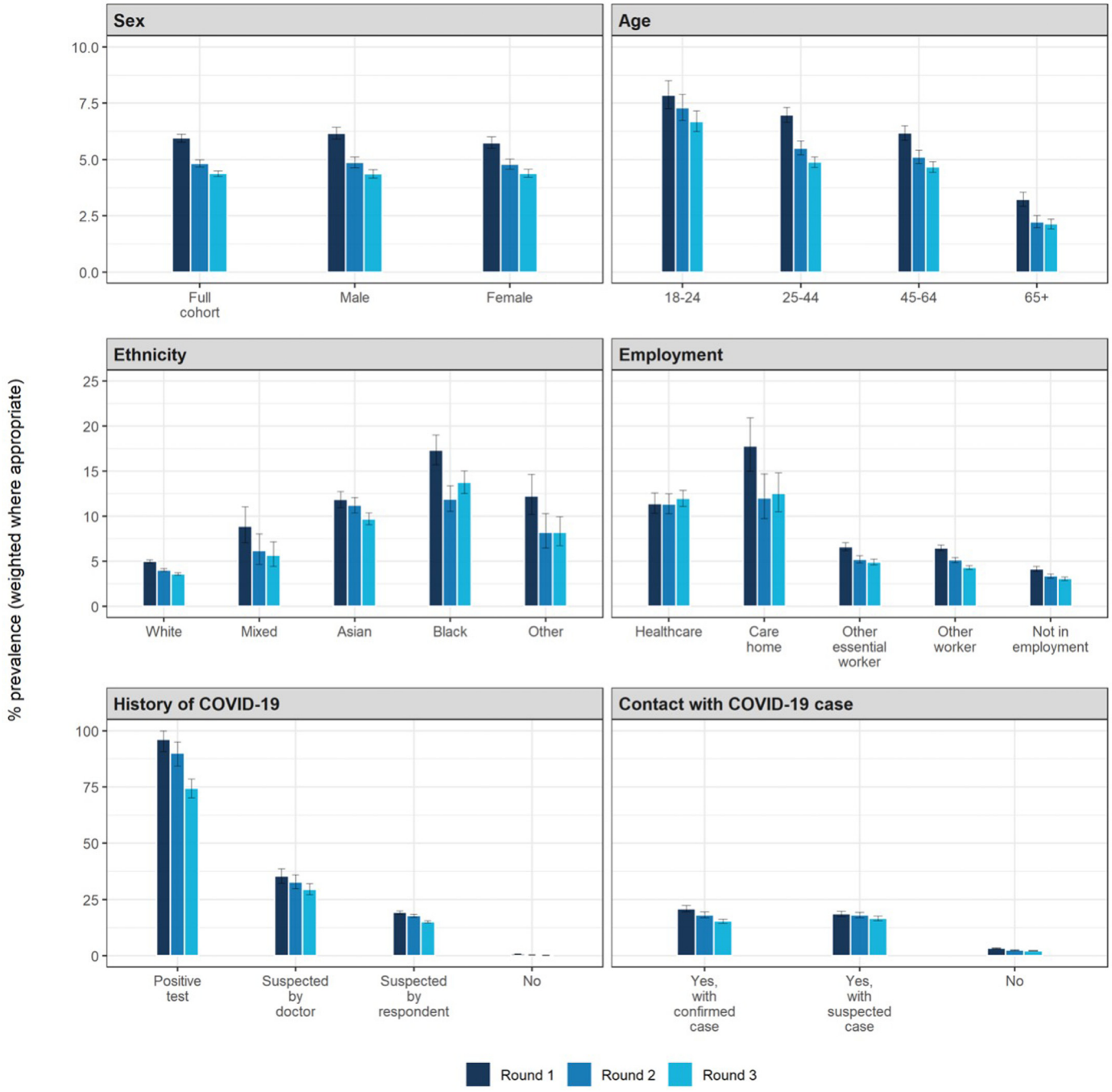

Fig. 1. Prevalence of antibody positivity to SARS-CoV-2 using LFIA test, by round of study (95% confidence intervals) by sex, age group, ethnicity, employment, history of COVID-19, symptom severity. Legend: Dates: Round 1 (20 June − 13 July 2020), Round 2 (31 July−13 August 2020), Round 3 (15−28 September 2020). Bars show antibody positivity by round of study for each category of covariate with 95% confidence intervals indicated in the error bars. NB: y axis scale is different for each row. All estimates of prevalence (95% confidence intervals) are adjusted for imperfect test sensitivity and specificity, and re-weighted to account for sample design and for variation in response rate (age, sex, ethnicity, region and deprivation) to be representative of the England population (18+). Full data shown in Supplementary Table S3.

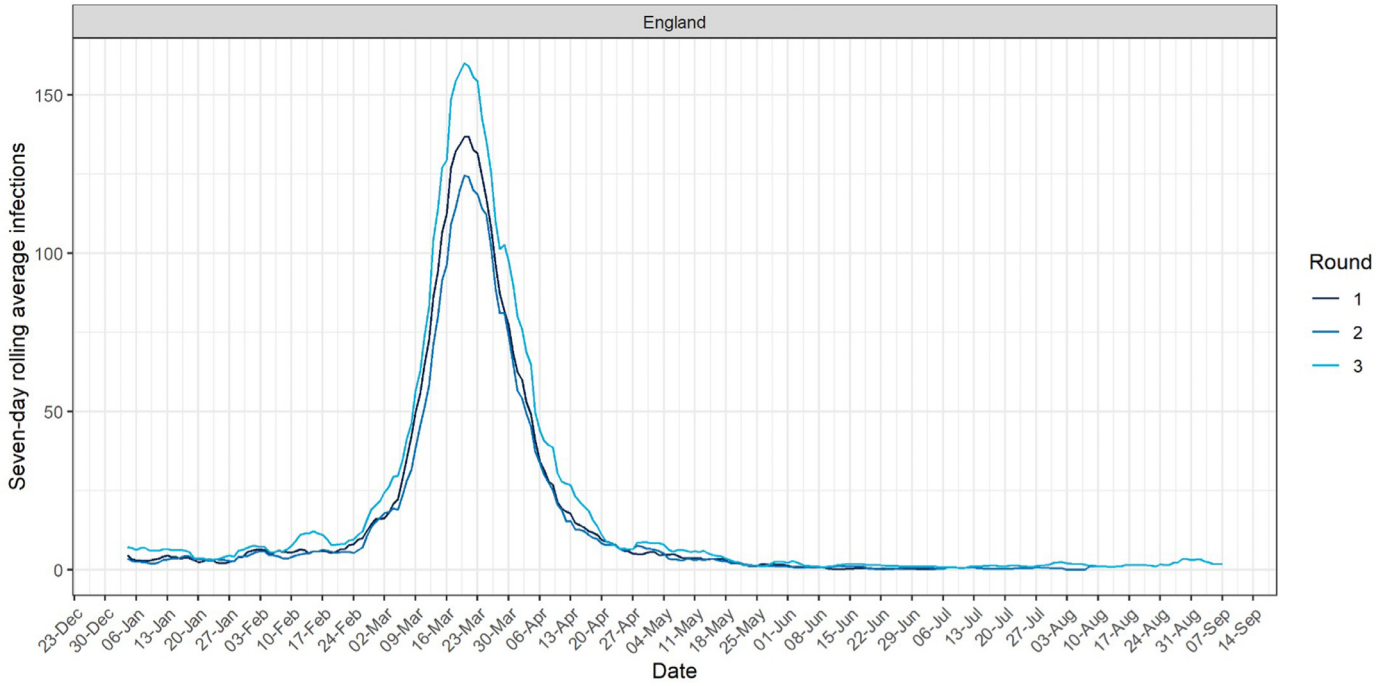

Fig. 2. Epidemic curve reconstructed from reported date of onset from 11,908 IgG antibody positive people who reported symptoms, by round of study[1]. Legend: Seven-day rolling average of number of infections (by day of onset) in 11,908 participants testing positive for antibodies and who reported a date of onset for symptoms of COVID19, shown separately for each round. 3,759 symptomatic cases were recorded in round 1 (from 99,908 tested); 3,363 were recorded in round 2 (from 105,829 tested); and 4,786 were recorded in round 3 (from 159,367 tested). [1] See Table 1 for dates of rounds.

against the spike protein (anti-S), but is qualitative rather than quantitative, and the threshold of detection is not stated in manufacturer's instructions. We tested serial dilutions of known positive sera on the LFIA and found that after differing dilutions the LFIA no longer yielded a positive band (Supplementary Figure S3). This suggests that, as antibody titres fall within a population with a diverse spread of starting titres, the proportion of the population with positive individual tests will decline. A key question is how the threshold for detection of antibody relates to the threshold required for protection from reinfection. Our data suggest the threshold for detection of antibody in sera with the LFIA corresponds to serum endpoint titres of 1:40 in a live virus microneutralisation assay. We cannot know at this time how this relates to the level of antibody that confers protection from infection, though studies in non-human primates vaccinated with an array of vaccines that conferred varying levels of immunity, suggest these may be similar levels to those required for protection [26]. While people that have lost their (neutralizing) antibodies are most likely susceptible to reinfection, it is entirely plausible that most of them are protected from severe disease due to specific T-cell and memory B-cells. There is some evidence that anti-S1 responses show faster rates of clearance than anti-NP, and therefore to monitor past infection should be combined with anti-NP serology, although it is anti-S1 measurements that correlate with near-contemporary pseudovirus neutralising antibody titres [27]. The relevant thresholds for protection in humans who are naturally exposed to SARS-CoV-2 remain to be defined and will continue to be informed by detailed studies of outbreaks [28].

There is emerging data on durable responses in several compartments of the adaptive immune system for up to six months, however, the contribution of persistent T cell immunity and memory responses to protective immunity remains unclear [29]. As such, while it is apparent that antibodies can protect against disease and infection, [24] it is not possible to say with certainty that the loss of antibody positivity in the LFIA would correlate with an increased risk of an individual being reinfected. However, at a population level, the waning we have observed may indicate an overall decline in the level of population immunity. Knowledge of the levels of infection in the population, levels of vaccination and ongoing risks of reinfection is key to understanding the future course of the epidemic.

Our study has limitations. It included non-overlapping random samples of the population, but it is possible that people who had been exposed to the virus were less likely to take part over time, which may have contributed to apparent population antibody waning. However, we

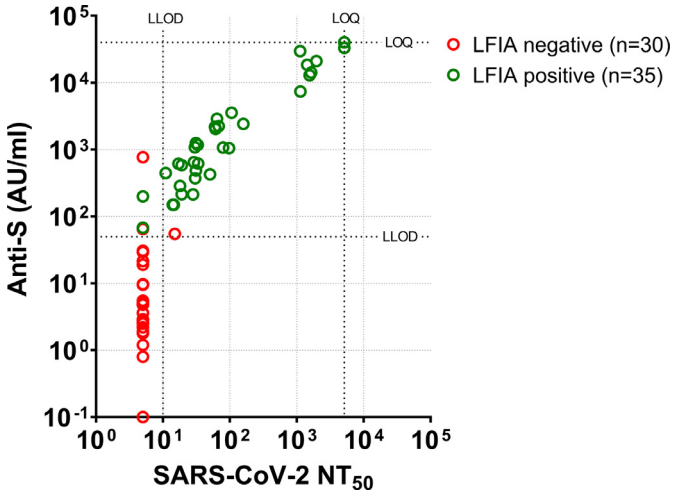

Fig. 3. Association of LFIA result with virus micro-neutralisation titre in 49 healthcare workers with RT-PCR-confirmed SARS-CoV-2 infection. Legend: Virus micro-neutralisation titre, log scale y-axis, by LFIA results, x-axis, in 49 healthcare workers with RT-PCR confirmed SARS-CoV-2 infection. Serum samples were assayed by live virus neutralisation assay and tested by Fortress LFIA. The median for those with a negative test (n=9) was less than 10 (lower limit of detection denoted by dotted line), and for those with a positive test (n=40) it was 1:40. Mann-Whitney test z-score =3.68, two-sided *P*= 0.00024. LFIA (lateral flow immunoassay).

had similar response rates and profiles across the three surveys and, for each round, we re-weighted the sample to be representative of the country as a whole. We adjusted for test characteristics (sensitivity, specificity) based on a clinic-based evaluation among healthcare workers with confirmed infection. Although this was carried out only before the first round, [12] changes in prevalence are unlikely to be a consequence of batch variation in tests. The declining prevalence of detectable antibodies raises the question as to the extent to which antibody prevalence estimated during the first round of our study, approximately three months after the peak of the first wave, may have underestimated the total of those infected in the first wave in England. We reported a prevalence of 6.0% (5.8, 6.1) from round one (20 June to 13 July 2020), implying that at least 3.36 (3.22, 3.51) million adults in England had been infected with SARS-CoV-2 [10]. Our first round estimate of antibody prevalence was consistent with a smaller study from the Office for National Statistics which reported antibody seroprevalence of 7.4% (5.6, 9.6) in May 2020 [30]. We compared the laboratory performance of the LFIAs used in rounds 1 and 2 (where we had seen the strongest decline in positive tests) and found no difference between the two rounds. We also did not detect differences in ability of participants to use the LFIA (indeed, failure rates were lower in later rounds compared to earlier ones). The characteristics of the test mean that results are not appropriate for clinical use in individuals and participants are advised not to change their behaviour based on the result. However, as participants are not blind to the results of their LFIA it is possible that this may have introduced bias into their questionnaire response, but this should not have affected our observation of declining prevalence over time.

In summary, our findings indicate that only a small proportion of the population of England (around 5 to 6%) had acquired detectable antibodies to SARS-CoV-2 on an LFIA test despite the high burden of infections and fatalities in the first wave. Our data provide evidence for a decline in naturally acquired antibody positivity within the population between June and September 2020. The current roll-out of a vaccination programme in England and other countries is aimed at achieving high levels of immunity at a population level.

Author Contributions

HW, GC, WB and PE designed the study and drafted the manuscript. MW, CA, MM, JCB, BF, AD, KA, AC conducted the analyses. JE reviewed the literature. HW, CA, GC, DA, CAD, WB, AD, GC, SR, PE provided study oversight. AD and PE obtained funding. All authors have reviewed and approved the final manuscript

Data availability

Supporting data for tables and figures are available on GitHub.

Declaration of Competing Interest

CAD reports grants from UK Medical Research Council, grants from UK NIHR, during the conduct of the study; HW and PE report grants from the Department of Health and Social Care during the conduct of this study. The remaining authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100098.

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