SHORT COMMUNICATION

Retrospective SARS-CoV-2 IgG screening during the first wave (March–June 2020) of the COVID-19 pandemic in the United Kingdom

Paul William Bird[1] [ORCID] | Kyran Sandhu[1] | Oliver Fletcher[1] | Billy Ames[1] | Oliver Toovey[2] | Julian Wei-Tze Tang[3]

[1]Department of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK

[2]Department of Clinical Virology, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK

[3]Department of Respiratory Sciences, University of Leicester, University of Leicester, UK

Correspondence
Dr. Julian Wei-Tze Tang, Department of Clinical Virology, University Hospitals of Leicester NHS Trust, Level 5 Sandringham Bldg, Leicester Royal Infirmary, Infirmary Sq, Leicester, LE1 5WW, UK.
Email: julian.tang@uhl-tr.nhs.uk

Abstract

During the "first wave" of the coronavirus disease 2019 (COVID-19) pandemic in the United Kingdom (March–June 2020), the city of Leicester was particularly hard hit, resulting in reimposed lockdown measures. Although initial polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was attempted within the community, testing was soon abandoned due to an inability to keep up with demand by local laboratories. It is therefore feasible that undiagnosed transmission of COVID-19 in the community by asymptomatic individuals was a real possibility. Therefore, retrospective SARS-CoV-2 immunoglobulin G (IgG) testing of archived sera from out-patients visiting University Hospitals of Leicester NHS Trust service was performed to investigate the transmission of SARS-CoV-2 in the community. A total of 1779 sera samples were tested from samples collected between 16th March and 3rd June 2020, of which 202 (11.35%) were SARS-CoV-2 IgG positive. Positivity was lowest in March (2.54%) at the beginning of the pandemic before peaking in April (17.16%) before a decline in May and June (11.16% and 12.68%, respectively). This retrospective screening offers some insight into the early patterns of SARS-CoV-2 transmission within a sampled community population during the first wave of the COVID-19 pandemic; supporting the argument for more community screening during high incidences of pandemics.

KEYWORDS
antiviral agents, coronavirus, immune globulin, SARS coronavirus, virus classification

1 | INTRODUCTION

During the early phase ("first wave") of the coronavirus disease 2019 (COVID-19) pandemic in the United Kingdom, nearly all diagnostic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was focused on polymerase chain reaction (PCR) testing for acute infections in symptomatic patients. This was primarily performed on patients admitted to the hospital with more clinically

severe acute COVID-19. An early attempt to perform SARS-CoV-2 PCR testing in the community on those who were less severely ill was soon abandoned by March 12, 2020 due to a lack of laboratory testing capacity.[1] This meant that people in the community were not being routinely screened for COVID-19 and that it was possible that patients presenting to the hospital for other reasons may have been infected with SARS-CoV-2 without being aware of this, particularly if any clinical illness was mild or asymptomatic.

This paper aims to investigate the prevalence of SARS-CoV-2 in the community by testing serum samples from out-patients presenting to the University Hospitals of Leicester NHS Trust for bloodborne virus screening.

2 | MATERIALS AND METHODS

To examine the prevalence of these undiagnosed, mildly or asymptomatic SARS-CoV-2 infections, we ran a search of 22 124 serum samples collected between 16th March and the 3rd June. Archived serum samples stored in chronological order were selected randomly (selecting every 17th sample to cover the time period and to keep within the limits of kits available for testing) and tested using the DiaSorin SARS-CoV-2 S1/S2 Assay (DiaSorin Ltd.) on the Diasorin Liaison XL automated platform, according to manufacturer's instructions.[2] The DiaSorin SARS-CoV-2 S1/S2 assay has a reported sensitivity of and specificity of 97% (95% confidence interval: 86.8%–99.5%) and 98.9% (97.5%–99.2%) which has been supported by the literature.[3]

The archived sera were originally collected during outpatient screening for bloodborne virus (human immunodeficiency virus [HIV], hepatitis B and C) status, or antenatal screening (hepatitis B, HIV, toxoplasma, syphilis), or other viral or bacterial screening for acute or latent infections (e.g., Epstein–Barr virus, cytomegalovirus, varicella-zoster virus, parvovirus, herpesviruses, galactomannan antigen, atypical pneumonia, and screens for amebic, filarial, schistosomiasis infections).

3 | RESULTS

Out of 1779 sera tested during this study period, 989 were from females (mean: 40.13, *SD*: 18.20, range: 0–99 years; 3 Chinese [Ch]/37 African [Af]/211 Asian [As]/732 Caucasian [Ca]/6 had no data [ND]) and 790 from males (mean: 52.02, *SD*: 19.08, range: 0–95 years; 10 Ch/41 Af/174 As/556 Ca/9 ND) patients (Figure 1A–C).

Of these, a total of 202 (202/1779, 11.35%) tested SARS-CoV-2 IgG positive:

March 16–31, 2020: 13/515 = 2.52% positives: 2/330 = 0.61% females, 1 Af/1 As; 11/185 = 5.95% males, 1 Af/2 As/7 Ca/1 ND.

April 1–30, 2020: 134/781 = 17.16% positives: 35/429 = 8.16% females, 2 Af/9 As/23 Ca/1 ND, with 1 As female testing equivocal; 99/352 = 28.13% males, 6 Af/34 As/58 Ca, 1 ND.

May 1–31, 2020: 46/412 = 11.16% positives: 15/200 = 7.5% females, 4 As/10 Ca/1 ND; 31/212 = 14.62% males, 2 Ch/13 As/16 Ca.
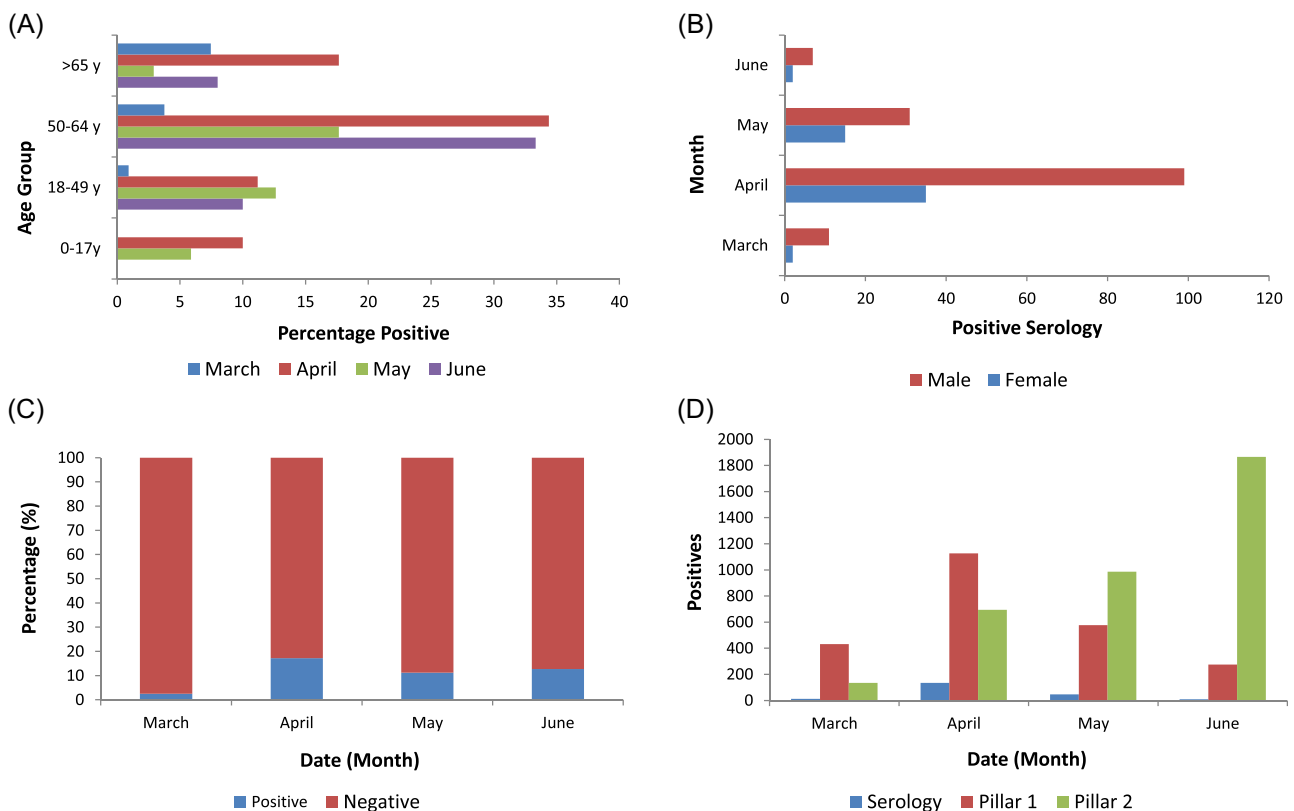

FIGURE 1   (A) Age-stratified SARS-CoV-2 IgG status in this Leicester cohort during March 16–30 June 2020. (B) Monthly SARS-CoV-2 IgG positive samples by gender. (C) Total (male and female) SARS-CoV-2 IgG status by month. (D) Monthly SARS-CoV-2 IgG positive samples compared to contemporary Leicester Pillar One and Pillar Two PCR positives. IgG, immunoglobulin G; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

June 1–3, 2020: 9/71 = 12.68% positives: 2/30 = 6.67% females, 2 Ca; 7/41 = 17.07% males, 1 Af/3 As/3 Ca).

4 | DISCUSSION

The large number of antenatal screening samples tested is reflected in the female:male ratio of these consecutive samples. These samples had been obtained from patients seen in hospital or outpatient clinics, most of whom had been tested for non-COVID-19-related reasons.

It can be seen the overall trend of the seropositivity follows the PCR positivity pattern during the first pandemic wave in the United Kingdom (March–June 2020; Figure 1D), which is not unexpected.

These 1779 samples also included sera from some acute COVID-19 cases who were also tested using SARS-CoV-2 PCR (AusDiagnostics Ltd.), performed in hospitalized patients.[4]

Out of the 1779 samples tested for SARs-CoV-2 IgG, 627/1779 = 35.24% also had a SARS-CoV-2 PCR test at some point. The timing of the serology test ranged from 227 days before to 104 days after the PCR test. Studies have shown considerable variation in time to seroconvert and length of time for waning neutralizing antibodies following infection. A study by Chia et al. (2021)[5] demonstrated an association between disease severity and long-term immunity, supporting the theory that asymptomatic or mild disease could result in a shorter period of immunity, which may have resulted in patients testing negative during this study. Of these patients who also had a SARS-CoV-2 PCR test performed, 155/627 = 24.72% were SARS-CoV-2 IgG positive and 472/627 = 75.28% were SARS-CoV-2 IgG negative.

So, of the 202 patients overall that tested SARS-CoV-2 IgG positive, 155/202 = 76.73% had also had a SARS-CoV-2 PCR test at some point. Of these, 107/155 (69.03%) tested PCR positive, with the timing of the PCR test ranging from 52 days before to 2 days after their SARS-CoV-2 IgG positive test, with the vast majority having their serology test on the day or after their PCR test (i.e., on Days 0–52 after their PCR test: 101/107 = 94.39%). Thus, most of the SARS-CoV-2 IgG positive results were likely consistent with a seroconversion response to a relatively recent, or current, ongoing SARS-CoV-2 infection.

Interestingly, 55/472 = 11.65% of the patients who tested negative for SARS-CoV-2 IgG tested positive by PCR at some point. The timing of the positive SARS-CoV-2 PCR test ranged from 18 days before to 182 days after the negative SARS-CoV-2 IgG test. Of these, 48/55 = 87.28%, therefore, did not show any detectable seroconversion for up to 18 days. This may not be surprising as studies have shown that SARS-CoV-2 IgG only becomes reliably detectable 10 days postillness onset.[6,7] We also do not know if these cases were symptomatic with COVID-19 symptoms at the time that the serum was taken.

One of the main limitations of this study is that we could not confirm the seropositive samples with a second serology assay. In a related study, we reported that during a period of low prevalence, even low levels of false-positive results (even with a highly specific assay) can become significant.[2] However, in this larger study during the high incidence of COVID-19 during the first pandemic wave in the United Kingdom, we believe that the serology results presented here are much more accurate.

Note that there is no reason for the patient demographics in this non-COVID-19, chronologically randomly selected, retrospective cohort to be similar to those of a typical COVID-19 patient population. The results reported here support the case for large scale community testing during pandemics and are supported in the literature, such as the Icelandic study by Gudbjartsson et al. (2020)[8] where over 30 000 Icelandic citizens were screened for anti-SARS-CoV-2 IgG, IgM, and IgA antibodies to determine the seroprevalence of the population. In the paper, the authors included 4222 quarantined citizens and 23 452 citizens with no symptoms or known exposure to SARS-CoV-2. The authors report a 2.3% seropositivity in the quarantined group and 0.3% in the unknown exposure group. Using this data and quantitative PCR (qPCR) data, they estimated that 0.9% of Icelanders were infected with SARS-CoV-2 and that 44% of persons infected with SARS-CoV-2 were not diagnosed with qPCR, estimates that can only be made through serological testing of large populations. However, several studies have urged caution over large scale testing due to the high levels of false positives during times of low prevalence.[2,9,10]

Our study also highlights the benefits of serological testing in the community to aid public health decisions, particularly when releasing people from quarantine or contact tracing following positive PCR results from a household member. In Peru, a rapid antibody testing team was employed to screen the population for IgM and IgG antibodies with those testing positive and having mild symptoms advised to quarantined. By May 2 over 350 000 people had been triaged, with over 26 000 by rapid testing leading to an alleviation of pressure on their healthcare system.[10] Serological testing in communities is also important for monitoring population risk of reinfection, the severity of disease, response to vaccination, and the need for booster shots and the response to variants.[11] The SIREN study in the United Kingdom is monitoring the immunological response in healthcare workers and demonstrated that previous history of SARS-CoV-2 leads to an 84% reduction in reinfection. Similar studies should be conducted in communities to improve risk assessment following infection and vaccination.[12]

There are warranted concerns over the effect new variants of SARS-CoV-2 may have on serological testing. The majority of serological assays target the nucleocapsid (N) protein and/or the spike (S) protein but some include the ORF8 and ORF3b.[13] The ORF8 is prone to nonsense mutations which can lower the sensitivity in assays that target the gene. Therefore, it is crucial that serological tests that either target multiple targets or using multiple tests in necessary to ensure cases are not missed.[2,13]

In conclusion, patients presenting routinely to the hospital from the community for other types of serology screening and retrospective test data offer some insight into the early pattern of SARS-CoV-2 transmission in the under-sampled community population,

during the first wave of the COVID-19 pandemic in this Leicester population.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Paul William Bird and Julian Tang Wei-Tze conceived the original study idea and performed the analysis of data. Paul William Bird, Kyran Sandhu, Oliver Fletcher, and Billy Ames performed the testing of samples. All authors discussed the results, reviewed and revised the drafts of the manuscript, and gave final approval to submit.

ORCID

Paul William Bird 🔟 https://orcid.org/0000-0002-5890-5262

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