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Short Communication

National population prevalence of antibodies to SARS-CoV-2 in Scotland during the first and second waves of the COVID-19 pandemic

N.E. Palmateer [a, b, *], E. Dickson [b], E. Furrie [c], I. Godber [d], D.J. Goldberg [a, b], P. Gousias [b], L. Jarvis [e], L. Mathie [b], S. Mavin [f], J. McMenamin [b], T.N. McNeilly [g], P. Murcia [h], J. Murray [b, i], G. Reid [b], C. Robertson [b, j], K. Templeton [k], B. von Wissmann [l], L.A. Wallace [b], C. Waugh [b], A. McAuley [a, b]

[a] Sexual Health and Blood-borne Viruses, Glasgow Caledonian University, Glasgow, United Kingdom
[b] Public Health Scotland, Glasgow, United Kingdom
[c] Immunology Laboratory Service, Blood Sciences, Ninewells Hospital, Dundee, United Kingdom
[d] Biochemistry Department, Queen Elizabeth University Hospital, Glasgow, United Kingdom
[e] Scottish National Blood Transfusion Service, Jack Copland Centre, Edinburgh, United Kingdom
[f] Scottish Microbiology Reference Laboratory, Inverness, United Kingdom
[g] Moredun Research Institute, Penicuik, United Kingdom
[h] Centre for Virus Research, University of Glasgow, Glasgow, United Kingdom
[i] Public Health, NHS Fife, Leven, United Kingdom
[j] University of Strathclyde, Glasgow, United Kingdom
[k] Department of Medical Microbiology, Royal Infirmary, NHS Lothian, Edinburgh, United Kingdom
[l] Public Health, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom

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ABSTRACT

Objectives: Studies that measure the prevalence of antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ('seroprevalence') are essential to understand population exposure to SARS-CoV-2 among symptomatic and asymptomatic individuals. We aimed to measure seroprevalence in the Scottish population over the course of the COVID-19 pandemic – from before the first recorded case in Scotland through to the second pandemic wave.
Study design: The study design of this study is serial cross sectional.
Methods: We tested 41,477 residual samples retrieved from primary and antenatal care settings across Scotland for SARS-CoV-2 antibodies over a 12-month period from December 2019-December 2020 (before rollout of COVID-19 vaccination). Five-weekly rolling seroprevalence estimates were adjusted for the sensitivity and specificity of the assays and weighted to reference populations. Temporal trends in seroprevalence estimates and weekly SARS-CoV-2 notifications were compared.
Results: Five-weekly rolling seroprevalence rates were 0% until the end of March, when they increased contemporaneously with the first pandemic wave. Seroprevalence rates remained stable through the summer (range: 3%–5%) during a period of social restrictions, after which they increased concurrently with the second wave, reaching 9.6% (95% confidence interval [CI]: 8.4%–10.8%) in the week beginning 28th December in 2020. Seroprevalence rates were lower in rural vs. urban areas (adjusted odds ratio [AOR]: 0.70, 95% CI: 0.61–0.79) and among individuals aged 20–39 years and 60 years and older (AOR: 0.74, 95% CI: 0.64–0.86; AOR: 0.80, 95% CI: 0.69–0.91, respectively) relative to those aged 0–19 years.
Conclusions: After two waves of the COVID-19 pandemic, less than one in ten individuals in the Scottish population had antibodies to SARS-CoV-2. Seroprevalence may underestimate the true population exposure as a result of waning antibodies among individuals who were infected early in the first wave.

The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Scotland was reported on 1 March 2020. The country has since experienced two waves of COVID-19 (the disease associated with SARS-CoV-2), which has resulted in one of the highest excess mortality rates worldwide. Estimates of the

* Corresponding author. Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA, United Kingdom.Tel.: (44)797 900 4363
E-mail address: norah.palmateer@phs.scot (N.E. Palmateer).

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proportion of individuals in the population who have been exposed to SARS-CoV-2 – both symptomatic and asymptomatic – are necessary to understand the progression of the pandemic to date. Because polymerase chain reaction (PCR) testing in the general population until recently has mainly been limited to those with symptoms, seroprevalence studies, which measure antibodies to SARS-CoV-2, provide a means of measuring population exposure. Furthermore, it is essential to have estimates of the extent of exposure from wild-type infection before rollout of vaccination. Most population-based seroprevalence surveys to date have focused on short time frames or subnational populations; here, we examine serial cross-sectional estimates of seroprevalence over a 12-month period in the Scottish general population, using residual blood samples from different sources.

Residual blood samples, originally collected for other purposes, were obtained from primary care (i.e. general practice) and antenatal care settings. Antenatal samples were retrospectively identified at regional laboratories across Scotland that store specimens taken for infectious disease screening at week 12 of pregnancy; these specimens are submitted from all antenatal settings in the regional health authority areas ('National Health Service (NHS) Boards') that are covered by these laboratories. Samples were available from International Organization for Standardization (ISO) week 1 (week beginning [w/b] 30th December 2019) to ISO week 26 (w/b 29th June 2020); all available samples with sufficient volume were included (totalling 16,157). Primary care samples were retrieved from regional laboratories, which receive samples from general practices across the NHS Boards that they cover. Approximately, 700 weekly samples were obtained between ISO week 17 (w/b 20th April 2020) and ISO week 53 (w/b 28th December 2020), totalling 25,320 samples. Primary care samples were selected according to an age/sex/NHS Board sampling frame corresponding to the Scottish general population structure. Eleven and seven of the 14 NHS boards in Scotland participated in the primary care and antenatal surveillance, covering 91% and 73% of the Scottish population, respectively. This analysis was restricted to samples up until the end of December 2020 to measure exposure to wild-type infection and not vaccine response: vaccination rollout for target groups began in Scotland on 8th December 2020; however, given the lag time between exposure to vaccination and seroconversion,[1,2] antibodies resulting from vaccine response would likely not be detectable in seroprevalence estimates until early January 2021.

Samples were anonymised before testing: only age (and sex for primary care samples) and the NHS Board were attached to the result. Primary care samples were sent to the Scottish Microbiology Reference Laboratory, where they were tested for the presence of anti-SARS-CoV-2 IgG antibodies using the LIAISON®SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Italy). Antenatal samples were tested at the regional laboratories where they were stored using either the Abbott (Abbott SARS-CoV-2 N IgG, Abbott, USA), Roche (Roche Elecsys Anti-SARS-CoV-2 N IgM/ IgG, Roche Diagnostics, Switzerland) or Siemens (Siemens Atellica IM 1300 S1 total antibody, Siemens Healthcare GmbH, Germany) assay, depending on the laboratory where testing was undertaken. We identified positive results in the antenatal samples in the weeks before the first confirmed case of COVID-19 in Scotland (n = 9). While there is evidence to suggest that COVID-19 was circulating before it was first identified in numerous countries,[3,4] we considered the possibility that these were false positives and therefore confirmatory testing was undertaken by retesting on a different assay (Roche/Siemens) to the original one (Abbott). Samples were retested (one retest per sample) in an ascending chronological order until 10 consecutive negative samples were obtained. The confirmatory result is presented here.

Local unpublished evaluations determined sensitivities and specificities of the assays (Table 1). Seroprevalence rates were adjusted for sensitivity and specificity[5] and weighted to a reference population (the Scottish general population for primary care; maternities in Scotland for antenatal), using bootstrap methods. Five-weekly rolling seroprevalence estimates were calculated to smooth out week-to-week variation; these were plotted against the last week in each five-week grouping (e.g. weeks 17–21 were plotted at week 21). Seroprevalence estimates were compared with SARS-CoV-2 PCR-positive notifications obtained from Public Health Scotland. Weekly totals for the latter were plotted against a 3-week lag to account for the delay between exposure to the virus and seroconversion (estimated to be between 2 and 4 weeks).[6] Chi-square tests for the trend (χ^2_{trend}) were conducted on the weekly unadjusted seroprevalence data to determine statistical significance. Mantel-Haenszel odds ratios, adjusted for ISO week, were calculated to examine differences in seroprevalence by sex, age group and region (categorized into urban/rural) among the primary care samples.

Rolling 5-weekly seroprevalence rates (Fig. 1a) in the antenatal samples were 0% from ISO weeks 5 (w/b Monday 27th January 2020) through to 13 (w/b Monday 23rd March) and then subsequently increased from 0.1% (95% confidence interval [CI]: 0.0%–0.3%) in ISO week 14 to 2.8% (95% CI: 2.2%–3.5%) in ISO week 20 (χ^2_{trend} = 14.72, P = 0.0001). The increase in seroprevalence occurred contemporaneously with the increase in SARS-CoV-2 PCR-positive cases associated with first wave of the COVID-19 pandemic in Scotland (Fig. 1b). Seroprevalence estimates were comparable between the two sources across the weeks where data were available from both (ISO weeks 21–26). The primary care seroprevalence estimates were stable across the period until approximately ISO week 43 (w/b 19th October 2020) (χ^2_{trend} = 0.41, P = 0.5241), at which point there was a sharp increase, reaching 9.6% (95% CI: 8.4%–10.8%) in ISO week 53 (w/b 28th December 2020) (χ^2_{trend} = 23.28, P < 0.001). This second increase in seroprevalence occurred concurrently with the increase in SARS-CoV-2 cases associated with the second wave of the pandemic (Fig. 1b).

Seroprevalence rates by sex, age and region are presented in the supplementary files. Seroprevalence between men and women (Fig. S1) was similar across the time series (P = 0.8318; Table S1). Seroprevalence was lower in the those aged 20–39 years and 60 years and older compared with those aged 0–19 years (P < 0.001 and P = 0.0013, respectively; Table S1, Fig. S2). Regional comparisons showed higher seroprevalence in NHS Boards with large urban centres compared with those with primarily rural populations (P < 0.001; Table S1, Figs. S3 and S4).

Our findings provide an indication of the general population exposure to SARS-CoV-2 in Scotland before the mass rollout of vaccination. To our knowledge, this is the first study to present national seroprevalence rates over two waves of infection. Our results are consistent with no population exposure in the early months of 2020 and a sharp increase in seroprevalence associated with onset of the first pandemic wave in March 2020. The stable seroprevalence rates thereafter coincide with a period of varying

Table 1
Sensitivities and specificities of the assays used to test samples for antibodies to SARS-CoV-2.

Assay	Sensitivity (95% CI)	Specificity (95% CI)	Samples tested
Abbott	95.5% (90.4%–98.3%)	99.8% (98.8%–100.0%)	Antenatal
DiaSorin	87.5% (78.2%–93.8%)	98.6% (97.0%–99.5%)	Primary care
Roche	92.3% (85.4%–96.6%)	100% (98.7%–100.0%)	Antenatal
Siemens	98.5% (95.7%–99.7%)	100% (98.4%–100.0%)	Antenatal

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CI, confidence interval.

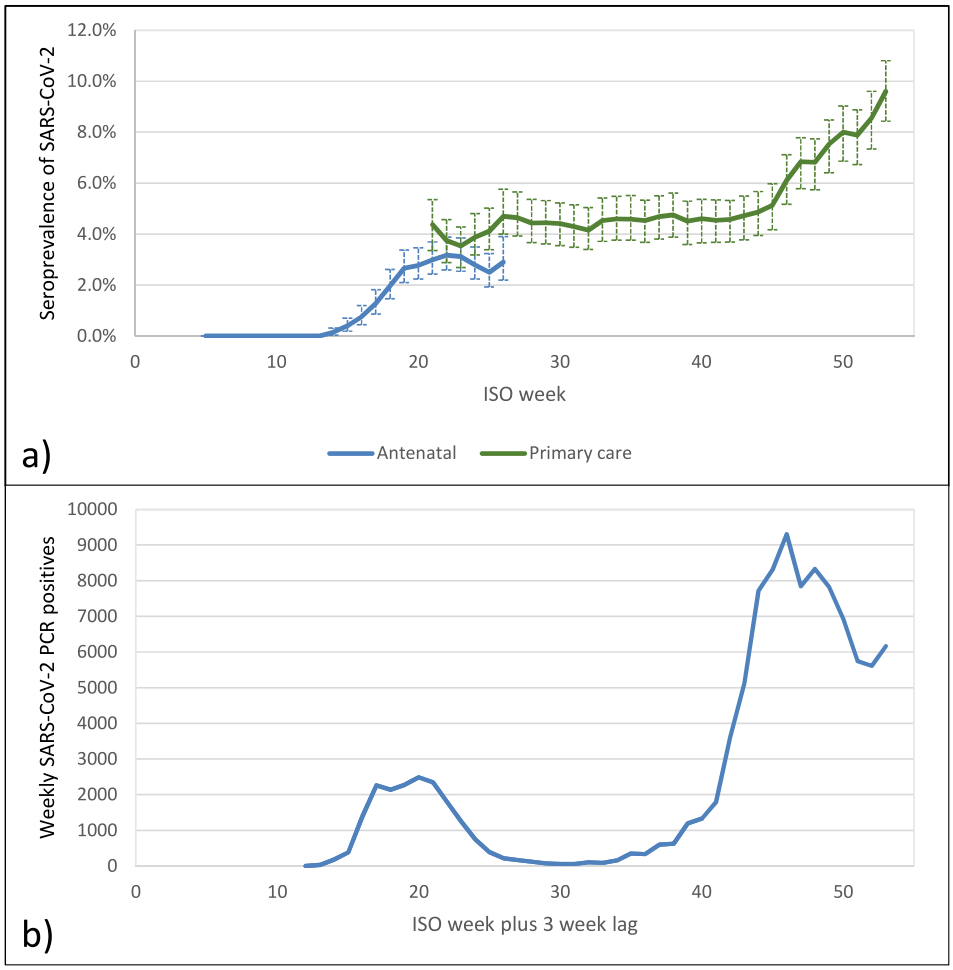

Fig. 1. Comparison of (a) 5-weekly rolling SARS-CoV-2 seroprevalence by source of residual samples with (b) confirmed weekly SARS-CoV-2 PCR positives reported to Public Health Scotland. Dashed lines indicate 95% confidence intervals. SARS-CoV-2 PCR positives have been plotted against ISO week +3 on the x-axis to account for the delay between exposure to the virus (infection) and formation of antibodies (seroconversion). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

intensity of social restrictions imposed from the first lockdown, on 23rd March, onward. A second sharp increase in seroprevalence was observed from October, coinciding with the second pandemic wave. Our seroprevalence findings are consistent with the PCR data during the period of restrictions from March to October; it is likely that the infection rates across this period, which otherwise would have caused an increase in seroprevalence, were counterbalanced by waning antibody among individuals who had been exposed early on in the pandemic.[7] We also found that seroprevalence rates were higher in urban areas and in those aged 0–19 years.

Despite two waves of infection, our estimate of seroprevalence of 9.6% at the end of December 2020 suggests that the majority of the Scottish population has still not been exposed to SARS-CoV-2. This finding is corroborated by seroprevalence data from other Western countries in similar phases of the pandemic: a study of blood donors/pregnant women in Stockholm, Sweden, showed approximately 15% seroprevalence by mid-December 2020 (this is comparable with our estimates from urban areas such as Greater Glasgow, which approached 13% by the end of December).[8] A household survey from Geneva found a slightly higher seroprevalence rate of 21%.[9]

Seroprevalence may, however, underestimate true population exposure for several reasons: lack of antibody persistence[7] and the role of other immune responses in neutralizing infection (there is evidence that some individuals who are exposed to SARS-CoV-2 do not develop measurable antibodies, suggesting the role of cellular immunity).[10] The ability of binding antibodies to confer immunity to SARS-CoV-2 infection is also not known, and antibody neutralisation activity may be less among asymptomatic individuals.[11]

Limitations of our study include the uncertainty in the sensitivity and specificity of the assays and uncertainty with regard to the representativeness of our samples with regard to the general Scottish population. To address this, we weighted the data to standard reference populations to account for any oversampling according to age, sex and geography; furthermore, primary care results are very consistent with data from a general household survey undertaken across Scotland.[12] The seroprevalence rates from antenatal samples were slightly lower than those from primary care: we hypothesise that pregnant women were taking extra precautions to avoid infection in the context of the COVID-19 pandemic.

Author statements

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Ethical approval

Approval for the COVID-19 serological surveillance work was given by the Head of Information Governance and Statistical Governance at Public Health Scotland.

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Competing interests

P.M. owns shares of Astra Zeneca. The remaining authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.07.006.

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