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## Article

# Repeated cross-sectional sero-monitoring of SARS-CoV-2 in New York City

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Daniel Stadlbauer<sup>1,10</sup>, Jessica Tan<sup>1,2,10</sup>, Kaijun Jiang<sup>1,10</sup>, Matthew M. Hernandez<sup>1</sup>, Shelcie Fabre<sup>3</sup>, Fatima Amanat<sup>1,2</sup>, Catherine Teo<sup>1</sup>, Guha Asthagiri Arunkumar<sup>1,2</sup>, Meagan McMahon<sup>1</sup>, Christina Capuano<sup>1</sup>, Kathryn Twyman<sup>8</sup>, Jeffrey Jhang<sup>9</sup>, Michael D. Nowak<sup>3,9</sup>, Viviana Simon<sup>1,4,5</sup>✉, Emilia Mia Sordillo<sup>3,9</sup>✉, Harm van Bakel<sup>6,7</sup>✉ & Florian Krammer<sup>1</sup>✉

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and has since caused a pandemic of Coronavirus Disease 2019 (COVID-19). The first COVID-19 case in New York City (NYC) was officially confirmed on March 1<sup>st</sup> 2020 followed by a severe local epidemic.<sup>1</sup> To understand seroprevalence dynamics, we conducted a retrospective, repeated cross-sectional analysis of anti-SARS-CoV-2 spike antibodies in weekly intervals from the beginning of February to July 2020 using more than 10,000 plasma samples from patients at Mount Sinai Hospital in NYC. Here we show the dynamics of seroprevalence in an ‘urgent care’ (UC) group, enriched for COVID-19 cases during the epidemic, and a ‘routine care’ group (RC), which more closely represents the general population. Seroprevalence increased at different rates in both groups, with seropositive samples as early as mid-February, and levelled out at slightly above 20% in both groups after the epidemic wave subsided by the end of May. From May to July seroprevalence stayed stable, suggesting lasting antibody levels in the population. Our data suggest an earlier than previously documented introduction of SARS-CoV-2 into NYC and describe the dynamics of seroconversion over the full course of the first pandemic wave in a major metropolitan area.

The first case of COVID-19 in NYC was identified at Mount Sinai Hospital on February 29, 2020 and confirmed on March 1, 2020.<sup>1</sup> A sharp rise in infections occurred shortly afterwards during the week ending on March 8, followed by a significant increase of COVID-19 deaths during the week ending on March 15 (Figure 1). New York State (NYS) implemented a stay-at-home order on March 22, 2020, after which daily case numbers in NYC started to plateau and then decreased in April and May 2020. Little nucleic acid amplification testing (NAAT) capacity was available at the beginning of the local epidemic in early March, and many asymptomatic and mild to moderate cases likely went undetected.

Although it is currently unknown if prior infection with SARS-CoV-2 can protect from reinfection, data from animal models as well as from studies with other human coronaviruses suggest that infection may confer immunity.<sup>2,3</sup> It is therefore important to determine the true infection rates in a population in order to assess how close this population is to potential ‘community immunity’.<sup>4</sup> Knowing the true infection rate also allows calculation of the infection fatality rate (IFR), which is likely much lower than the case fatality rate (CFR). To estimate true infection rates, serosurveys can be used that measure the presence of antibodies

to past virus infections, rather than the presence of virus.<sup>5</sup> Serological assays for measuring antibodies to SARS-CoV-2 rely either on the viral nucleoprotein, the spike protein on the virus surface, or the receptor binding domain (RBD), which is an important part of the spike protein that interacts with angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2.<sup>6</sup> We have recently established a two-step enzyme-linked immunosorbent assay (ELISA) in which serum/plasma samples are prescreened at a set dilution for reactivity to RBD. Positives in this first step are confirmed and the antibody titer is assessed in a second ELISA against the full-length spike protein.<sup>7,8</sup> The use of two sequential assays reduces the false positive rate and favors high specificity resulting in a sensitivity of 95% and a specificity of 100% (Extended Data Table 1).

## Serosurvey strategy

In the week of February 9, 2020, we started to collect residual, random, de-identified, cross-sectional plasma samples originally obtained for standard of care medical purposes. These samples were divided into two distinct groups. The first group included samples from patients

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# Article

seen in Mount Sinai's emergency department (ED) and from patients that were admitted to the hospital for urgent care during the period beginning with the week ending on February 9 through the week ending on July 5. This group, termed the 'urgent care' (UC) group, served as a positive control group designed to detect increasing SARS-CoV-2 infections since we assumed that individuals with moderate to severe COVID-19 would seek care at the ED and be admitted to the hospital at increasing rates as the local epidemic progressed. The second group of samples, termed the 'routine care' (RC) group, were obtained from patients at OB/GYN visits and labor and deliveries, oncology-related visits, as well as hospitalizations due to elective surgeries, transplant surgeries, pre-operative medical assessments and related outpatient visits, cardiology office visits, and other regular office/treatment visits. We reasoned that these samples might resemble the general population more closely because the purposes for these scheduled visits were unrelated to COVID-19. The UC group comprised 45.5% females while the RC group included 67.6% females (Table 1). The majority of individuals in the UC group were  $\geq 61$  years of age while the RC group had a more balanced age distribution that more closely resembled the general population, albeit with the 0–20 year age group being severely underrepresented (Table 1). Except for the weeks ending February 9 and February 16, for which only 16 samples were obtained across the two weeks (3 in the UC, 13 in the RC group), the UC group size ranged between 168 and 274 samples per week and the RC group included 231–493 samples per week (Extended Data Table 2 and 3). A total of 10,691 samples obtained between the weeks ending February 9 and July 5 were tested: 6,590 samples in the RC and 4,101 in the UC group.

## Seroprevalence in the UC group

In the UC group, no sero-positives were detected in the weeks ending on February 9 and 16, and low seroprevalence was found during the weeks ending on February 23 to March 15 (ranges between 1.4 and 3.2%, Figure 1a). A sharp increase to 6.2% was detected in the week ending on March 22, concurrent with the uptick in new confirmed SARS-CoV-2 infections and related hospitalizations. This increase continued in the weeks ending on March 29 (17.4%), April 5 (46.7%) and April 12 (56.7%). Seroprevalence in this group peaked at 61.7% in the week ending on April 19, then started to decline to 21.9% in the week ending on May 24 and stayed flat thereafter, matching the decrease in new COVID-19 diagnoses. For many samples in the UC group, NAAT results for SARS-CoV-2 infection were available and the rate of positivity in nasopharyngeal swab specimen tracks well with seropositivity (Extended Data Fig 1). The seroprevalence values we report reflect hospital admissions due to COVID-19, although the uptick in positive serology results lagged approximately 1–2 weeks behind the increased number of SARS-CoV-2 infections confirmed by NAAT. This is expected since there is usually a delay between acute infection and seroconversion.

## Seroprevalence in the RC group

Similar to the UC group, the seroprevalence found in the RC group was very low during the weeks ending on February 9 through March 29 (0% to 2%, Figure 1b). Of note, some samples during that time had moderately high reactivity (endpoint titers of 1:150–1:400) (Figure 1d). An increase in seroprevalence from 1.6% to 2.2% was detected in the week ending on March 29, with 10.1% and 11.7% in the following weeks, reaching 19.1% seroprevalence in the week ending on April 19. From April 19 to July 5, the seroprevalence stabilized at the 20% level in the RC group, while the number of confirmed COVID-19 cases in NYC rapidly declined (Extended Data Fig 2A). Interestingly, the delay between the sharp increase in SARS-CoV-2 detection by NAAT in NYC (Figure 1e) and the increase in seroprevalence in the RC group is longer than the delay between the increase in confirmed cases and the increase in seroprevalence in the UC group (Figure 1a, b). This may be attributed to different

antibody kinetics in mild cases which are often delayed as recently shown<sup>9–13</sup> and which likely constitute the majority of infections in the RC. We also analyzed the increase in seroprevalence over the observation period as compared to cumulative official case numbers. Although there is an overall good agreement, the curve fit for the increase in seroprevalence seems to have a steeper slope than the cumulative case curves (Extended Data Fig 2C).

The antibody titers detected in both groups were initially lower and gradually increased to titers as high as 1:51,200 (Figure 1c, d). Overall, the titers in the UC group were significantly higher than in the RC group (Figure 1f), which is likely a function of disease severity in individuals in the UC group. Of note, SARS-CoV-2 spike antibody titers detected in the RC specimens were stable from April 5 onwards (Extended Data Fig 2B) although the seroprevalence did not increase further after April 19, and recorded case numbers declined (Extended Data Fig 2A), indicating that there was no appreciable waning of SARS-CoV-2 S-specific IgG in the community over this time frame.

## Seroprevalence in different subgroups

In order to determine which patient subgroup(s) were driving the rise in seroprevalence, we further divided the RC group into four subgroups: (i) "OB/GYN" visits and labor and deliveries ( $n=2,643$  samples); (ii) "Oncology" visits and treatment hospitalizations ( $n=2,592$ ); (iii) "Surgery", including various elective surgeries, transplant surgeries, pre-op medical assessments and related visits ( $n=1,072$ ); and, (iv) "Cardiology", including cardiology office visits and other regular office/treatment visits ( $n=283$ ). The rise in seroprevalence was mostly driven by "OB/GYN" visits and labor and deliveries, which showed an early increase in seroprevalence in the week ending on March 29 (2.8%) followed by continued rise to 9.6%, 15.6% and 26.8% in the weeks ending on April 5, April 12 and 19, respectively and stabilized thereafter at 24.5% in the week ending on May 24 maintaining a seroprevalence of about 20% until the week ending on Jul 5 (Figure 2a). Seroprevalence in "Oncology" patients increased during the same time frame, but more slowly and steadily, reaching 19.0% in the week ending with Jul 5 (Figure 2b). Similar seroprevalence trends were observed in the "Surgery" and "Cardiology" and other office visits subgroups, although the small number of specimens – partially driven by a pause in elective hospital procedures and surgeries due to the pandemic in April and May - limited conclusions for these subgroups individually since confidence intervals were very wide (Figure 2c, d).

## Discussion

Our study provides a window into the extent of seroprevalence in NYC throughout the first wave of the SARS-CoV-2 pandemic when the city emerged as an early epicenter. Although our specimen sampling approach results in a biased representation of the entire metropolitan area, it provides valuable insights on the dynamic nature of SARS-CoV-2 antibody responses at the population level.

The UC group was designed as positive control group that would become enriched in seropositive individuals during an epidemic since acute SARS-CoV-2 infected individuals would seek care in the ED and would be admitted to the hospital in large numbers. As anticipated, a very high seroprevalence and a rapid increase in titers was detected in this group due to the dramatic upsurge in SARS-CoV-2-related ED visits and admissions between February–April 2020. During that phase of the epidemic in NYC, the seroprevalence and percent of NAAT positives tracked well in the group. If no or very few new cases of SARS-CoV-2 occur, the seroprevalence in this group should drop and track closely with the seroprevalence in the general population, which is what we observed in the end of May until beginning of July. While this group cannot be used to determine general seroprevalence during a pandemic,

it confirmed that our serosurveillance was working and increased our confidence in the results of the RC group. Including similar enriched, positive control groups into serosurveillance studies, especially in the beginning of an outbreak, could be valuable to validate serological methods. On its own, monitoring seropositivity of ED and admitted patients might also be a valuable tool to track an epidemic if NAAT is not available.

In contrast, the RC group was designed to resemble the NYC population more closely, albeit with several caveats: 0-20 year olds were underrepresented, (5.4% versus 25.9%), above-61 year olds were overrepresented (31.0% versus 16.1%, Table 1) and females were also overrepresented (67.6% versus 52.5%) as compared to the city's population. Additional biases include that vulnerable individuals (e.g. pregnant women and cancer patients) were likely more cautious to avoid exposure to the virus. Conversely, due to their need to access medical care during the lockdown period, their risk for virus exposure may also have increased. The seroprevalence in this group consequently may be either an underrepresentation or overrepresentation of the seroprevalence in the general population.

The seroprevalence that we found in the RC group is consistent with data from Columbia University reporting that 15.4% of pregnant women who delivered infants at their facilities between March 22 and April 4, 2020 were infected with SARS-CoV-2<sup>14</sup>. This tracks well with seroprevalence in the RC group, which was between 10.1 and 19.1% in the weeks following April 5. A serosurvey conducted by the NYS Department of Health (NYSDOH) determined that between April 19 and 28, the seroprevalence for SARS-CoV-2 in the NYC metropolitan region was 22.7%,<sup>15</sup> matching very well with the data for our RC group from the week ending on April 19. Finally, a study by the US CDC found a seroprevalence of 6.9% in NYC in samples obtained between March 23 and April 1.<sup>16</sup> During this time frame (weeks ending on March 22- April 5), we saw an increase from 1.6% to 10.1%. While all three of these single-time point studies used different methodologies and samples, the seroprevalence in our RC group agrees astonishingly well with their results and indicates that this group, despite suffering from heavy biases, likely reflects seroprevalence in NYC relatively well.

The first seropositive samples in our study were already detected during the week of February 23, one week before the first confirmed SARS-CoV-2 case in NYC was identified suggesting that SARS-CoV-2 was likely introduced to the NYC area several weeks earlier than previously assumed. This would not be unexpected given the unique diversity and connectivity of NYC and the large numbers of travelers that were arriving from SARS-CoV-2 affected regions of the world in January and February of 2020. The antibody titers of initial positives were low, which is consistent with slower seroconversion of perhaps mild cases.<sup>9-13</sup> Of course, we cannot exclude with absolute certainty that some of the lower positive titers are false positives since the initially low seroprevalence falls within the confidence intervals of the PPV.

Of note, the seroprevalence in the RC group (as well as the UC group in the end of May, post peak) falls significantly below the threshold for potential community immunity, which has been estimated by one study to require at least a seropositivity rate of 67% for SARS-CoV-2.<sup>4</sup> Based on the population of NYC (8.4 million), we estimate that by the week ending May 24, approximately 1.7 million individuals had been infected with SARS-CoV-2. Taking into account the cumulative deaths in the city by May 19 (16,674), this suggests a preliminary IFR of 0.97% (with the assumption that both seroconversion and death occur with similar delays). This is in stark contrast to the IFR of the 2009 H1N1 pandemic which was estimated to be 0.01%-0.001%.<sup>17</sup>

A very unique aspect of our study is that it provides important information about the dynamics of SARS-CoV-2 seroconversion and the stability of antibody responses before, during and after the first epidemic peak in an early and major epicenter of the pandemic. Our dataset will

be useful to generate models that can then more accurately predict dynamics of seroprevalence in other geographic locations, even if serosurveys in these locations are based on few, widely spaced points in time. Our study further underscores the value of serological testing, even when done retrospectively, to capture the onset and full extent of a pandemic wave when there is limited capacity for NAAT. While phylogenetic analysis of later isolates can provide estimated times of introductions, these estimates do have large confidence intervals. A combination of both serology and phylogenetic analysis using precision surveillance is likely the most accurate and useful tool to determine the true onset of an epidemic.

We will continue this repeated cross-sectional serosurvey for at least one year, and expect that, if antibody titers remain stable, the seroprevalence would likely not change significantly unless new infections rise again or vaccines would become available.

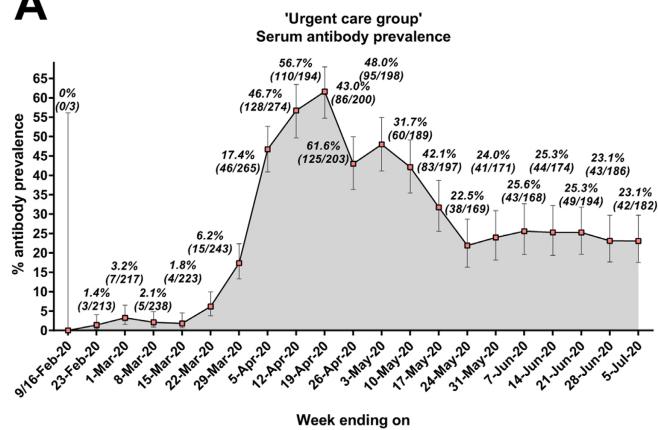
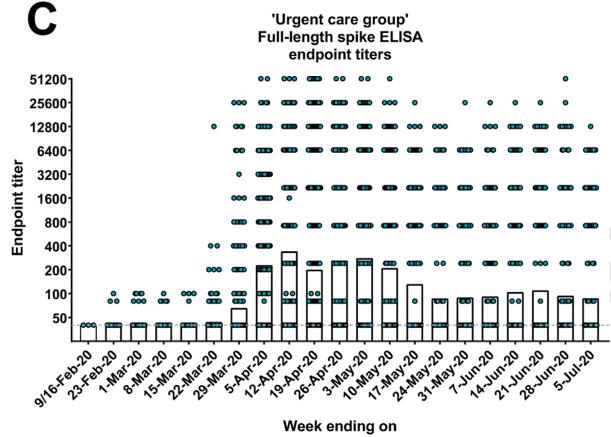
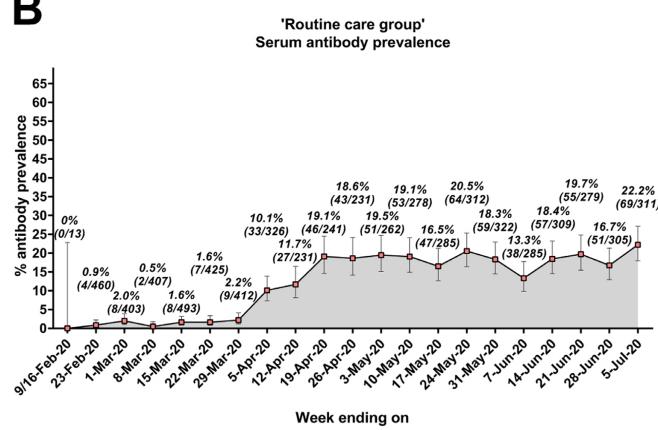
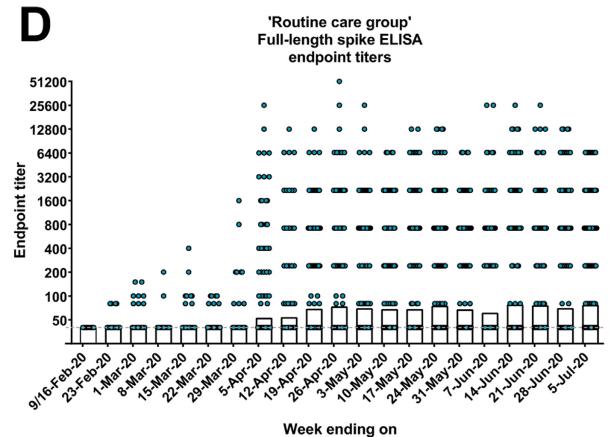
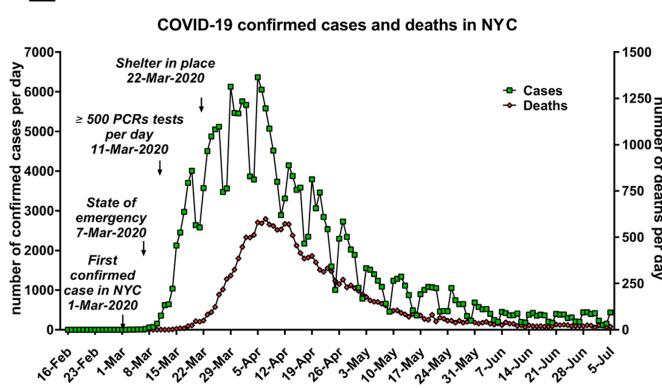
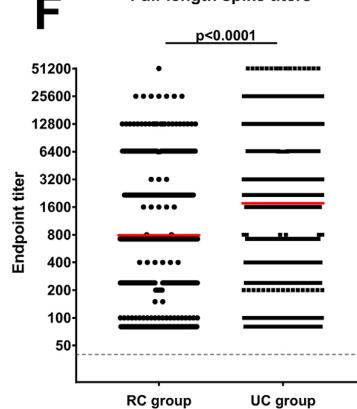
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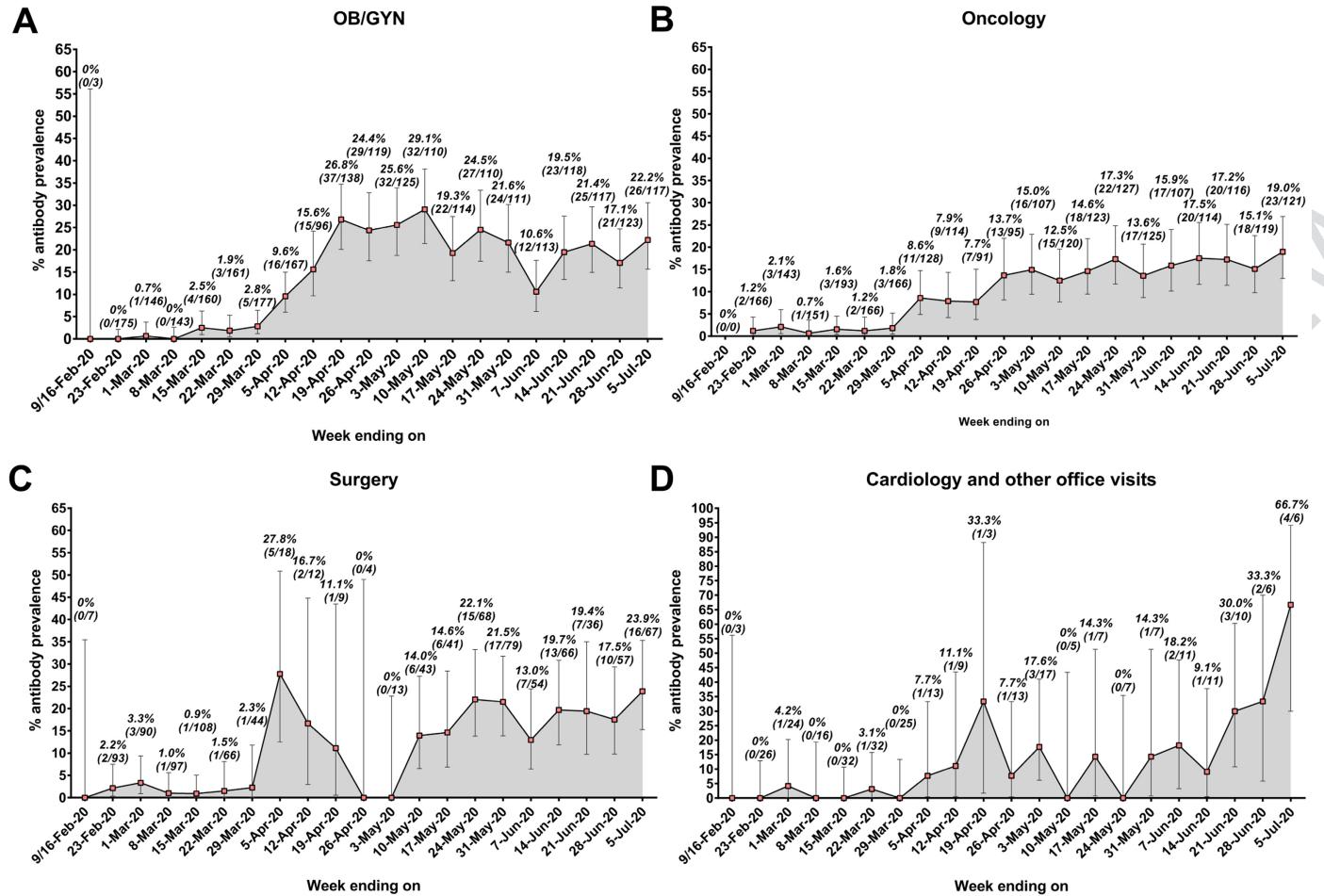
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**Fig. 1 | Seroprevalence, full-length spike antibody titers and confirmed cases in NYC.** (A) Serum antibody prevalence in the urgent care group between the weeks ending February 9 (first two weeks combined) to July 5, 2020. (B) Serum antibody prevalence during that same timeframe in the routine care group. (C) Full-length spike antibody titers in the urgent care group in the sampled time period. (D) Spike endpoint titers in the routine care group. The bars represent the geometric mean. (E) Confirmed cases and deaths in NYC in the early weeks of the SARS-CoV-2 epidemic. (F) Comparison of endpoint titers

in the RC ( $n=733$ ) and UC ( $n=1067$ ) groups. Red lines indicate the geometric mean.  $P$ -Value from two-tailed Mann-Whitney U test. Data for confirmed COVID-19 cases and deaths in NYC was retrieved from <https://www1.nyc.gov/site/doh/covid/covid-19-data.page>. Each plasma sample was tested once. Sample numbers per week are indicated directly in the figure. Line in A and B represent the mean and error bars represent the 95% confidence intervals, bars in C and D represent geometric mean titers.



**Fig. 2 | Seroprevalence in the different screening subclasses over time.**

Seroprevalence for OB/GYN (A), surgery (B), oncology (C) and cardiology and related office visits (D) groups in the weeks ending February 9 (first two weeks

combined) to Jul 5, 2020. Sample numbers per week are indicated directly in the figure. Error bars represent the 95% confidence intervals. Each plasma sample was tested once.

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**Table 1 | Demographic characteristics, seroprevalence and COVID-19 diagnosis in different study populations**

Population	n	Female	Age group				Antibody positive	COVID-19 diagnosis	Description
			0-20	21-40	41-60	≥61			
<b>'Routine care group'</b>									
OB/GYN	2643	2551 (96.5%)	236 (8.9%)	2148 (81.3%)	229 (8.7%)	30 (1.1%)	354 (13.4%)	319 (13.9%)	OB/GYN visits and deliveries
Oncology	2592	1210 (46.7%)	89 (3.4%)	418 (16.1%)	718 (27.7%)	1367 (52.7%)	240 (9.3%)	225 (8.7%)	Oncology visits and treatment hospitalizations
Surgery	1072	549 (51.2%)	28 (2.6%)	163 (15.2%)	360 (33.6%)	521 (48.6%)	114 (10.6%)	47 (4.4%)	Surgeries, transplant surgeries, pre-op medical assessments and related visits
Cardiology and other office visits	283	142 (50.2%)	5 (1.8%)	79 (27.9%)	74 (26.1%)	124 (43.8%)	23 (8.1%)	11 (3.9%)	Cardiology office visits and other regular office/treatment visits
<b>Subtotal</b>	<b>6590</b>	<b>4452 (67.6%)</b>	<b>358 (5.4%)</b>	<b>2808 (42.6%)</b>	<b>1381 (21.0%)</b>	<b>2043 (31.0%)</b>	<b>731 (11.1%)</b>	<b>602 (9.1%)</b>	
<b>'Urgent care group'</b>									
Inpatient	4101	1864 (45.5%)	115 (2.8%)	616 (15.0%)	1185 (28.9%)	2185 (53.3%)	1067 (26.0%)	967 (23.6%)	Emergency department and inpatient admissions
<b>General population New York City</b>									
New York City	8,175,133	4,292,589 (52.5%)	2,115,286 (25.9%)	2,626,489 (32.1%)	2,118,676 (25.9%)	1,314,682 (16.1%)	N/A	N/A	2010 Decennial census New York City

## Methods

### Study participants and human samples

Residual EDTA-anticoagulated blood specimens remaining after standard of care testing were obtained from the MSH Blood Bank and sorted by collection date, location, and by patient practice category (OB/GYN visits and labor and deliveries; oncology visits; surgeries and related visits; Cardiology office/treatment visits; ED visits; and other related hospital admissions). To select samples in an unbiased manner, plasma samples were selected randomly from up to the first 152 specimens for each location per collection week, and aliquoted for testing. All test samples were logged into a de-identified database and matched to anonymous patient identifiers and verified patient categories, after which duplicate samples obtained from the same patient within one week were retrospectively removed from further analysis. Samples from the same patient were included in the analysis if they were collected at least seven days apart. If seven days or more apart, seroconversion could potentially occur and we therefore consider this small number of specimens as an independent sample of the population. Collection started in the week ending February 9, 2020. Between 231–493 plasma samples per week (starting from the week ending on February 23, 2020) were selected from the 'RC' patient setting from patients that went for OB/GYN visits and labor and deliveries, oncology visits, surgeries and related visits as well as cardiology office visits and other regular office visits (see Extended Data Table 1 for detailed numbers and breakdown per cohort). Approximately 200 plasma samples per week were selected from an inpatient cohort setting, consisting of plasma from patients that were admitted to the emergency department and other related hospital admissions ('UC'). For some individuals, a PCR test for viral RNA was performed to diagnose COVID-19 infection.

This study (protocol HS# 20-00308) was reviewed by the Mount Sinai Health System Institutional Review Board, Icahn School of Medicine at Mount Sinai, and determined to be exempt human research as defined by Department of Health and Human Services (DHHS) regulations (45 CFR 46.104). The collection and testing of residual plasma specimen was performed in a blinded manner, and all data used in this study was anonymized following local and reporting regulations through the use of an honest broker.

### Recombinant proteins

The recombinant RBD and spike protein of SARS-CoV-2 were generated and expressed as previously described.<sup>7,8</sup> In brief, the mammalian cell codon-optimized nucleotide sequences for RBD (amino acids 319–541) including a signal peptide and hexahistidine tag or the soluble version of the spike protein (amino acids 1–1,213) including a signal peptide, C-terminal thrombin cleavage site, T4 foldon trimerization domain and hexahistidine tag were cloned into the mammalian expression vector pCAGGS. The nucleotide sequence of the spike protein was additionally modified to remove the polybasic cleavage site and two stabilizing mutations were introduced. The expression plasmids are available at BEI Resources Repository (<https://www.beiresources.org/>).

Recombinant proteins were produced in Expi293F cells (Thermo Fisher) using the ExpiFectamine 293 Transfection Kit (Thermo Fisher) according to manufacturer's instructions. Expi293F cells were not authenticated and tested negative for mycoplasma. Proteins were purified by gravity flow using Ni-NTA Agarose (Qiagen) and concentrated in Amicon centrifugal units (EMD Millipore). Purified proteins were analyzed by reducing sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and correct folding was confirmed by performing ELISAs with RBD-specific monoclonal antibody CR3022<sup>18,19</sup> or 2B3E5.

### Enzyme-linked immunosorbent assay (ELISA)

The serological assays were performed as previously described in detail following a two-step ELISA protocol.<sup>7,8</sup> The assay used here has a workflow that closely resembles an assay established in the Mount

Sinai Health System (MHS) CLIA-certified Clinical Pathology Laboratory, which received an FDA Emergency Use Authorization (EUA) in April 2020. However, the assay used in this study was performed in a research laboratory setting with a sensitivity of 95% and a specificity of 100% (Extended Data Table 1) resulting in a positive predictive value of 1 (PPV, 95% confidence interval (CI): 0.908–1.000) and a negative predictive value of 0.97 (NPV, 95% CI: 0.909–0.995).

In the first step, plasma samples were screened in a high-throughput assay using the recombinant RBD protein. Ninety-six-well microtiter plates (Thermo Fisher) were coated with 50 µL recombinant RBD protein at a concentration of 2 µg/mL overnight at 4 °C. The next day, the plates were washed three times with PBS (phosphate-buffered saline; Gibco) supplemented with 0.1% Tween-20 (T-PBS; Fisher Scientific) using an automatic plate washer (BioTek). The plates were blocked with 200 µL blocking solution consisting of PBS-T with 3% (w/v) milk powder (American Bio) and incubated for 1 h at room temperature. As a general safety precaution, plasma samples were heat inactivated for 1 h at 56 °C. The blocking solution was thrown off the plates and 100 µL of plasma samples diluted 1:50 in PBS-T containing 1% (w/v) milk powder were added to respective wells of the microtiter plates. After 2 h the plates were washed three times with PBS-T and 50 µL anti-human IgG (Fab-specific) horseradish peroxidase antibody (HRP, produced in goat; Sigma, #A0293) diluted 1:3,000 in PBS-T containing 1% milk powder was added to all wells and incubated for 1 h at room temperature. The microtiter plates were washed three times with PBS-T and 100 µL SigmaFast o-phenylenediamine dihydrochloride (OPD; Sigma) was added to all wells. The reaction was stopped after 10 min with 50 µL per well 3M hydrochloric acid (Thermo Fisher) and the plates were read at a wavelength of 490 nm with a plate reader (BioTek). Plasma samples that exceeded an OD<sub>490</sub> cutoff value of 0.15 were categorized as presumptive positives and were tested in a second step in confirmatory ELISAs using full-length, recombinant spike protein.

To perform the confirmatory ELISAs, the plates were coated and blocked as described above except full-length spike protein at a concentration of 2 µg/mL was added to the plates. After 1 h the blocking solution was removed, presumptive positive plasma samples serially diluted in 1% milk prepared in PBS-T were added and the plates incubated for 2 h at room temperature. The remainder of the assay was performed as described above. The data were analyzed in Microsoft Excel and GraphPad Prism 7. The cutoff value was set as an OD<sub>490</sub> of 0.15 and true positive samples were defined as samples that exceeded an OD<sub>490</sub> value of 0.15 at a 1:80 plasma dilution. The endpoint titer was calculated and defined as the last dilution before the signal dropped below an OD<sub>490</sub> of 0.15. For samples that exceeded an OD<sub>490</sub> of 0.15 at the last dilution (1:12,800 for samples of weeks ending on March 29 and April 5; 1:6,480 for samples of weeks April 12 and May 24), a four-parameter curve fit (variable slope) was applied and the endpoint titer determined by interpolation.

The sensitivity and specificity of the assay were determined using a panel of serum and/or plasma of 40 patients that had PCR-confirmed SARS-CoV-2 infection (true positives) and 74 negative control samples (56 samples that were taken before the pandemic and 18 samples without confirmed SARS-CoV-2 infection; true negatives). The PPV and NPV were determined taking into account the ratio of true positives and true negatives (seroprevalence of 35%) in the panel. Importantly, using the 100% specificity determined using the panel and assuming a low (e.g. 1%) true seroprevalence in the test group would not change the PPV.

### Statistical analysis

The 95% CI of the seroprevalence was calculated assuming binomial data based on methods by Wilson/Brown.<sup>20</sup> Significant differences in endpoint titers between the urgent care and routine care groups were identified by the Mann-Whitney U test. The 95% CI for assay sensitivity, specificity, positive predictive value and negative predictive value were determined using methods by Wilson/Brown.

# Article

## Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

## Data availability statement

Raw data for Figures 1 and 2 has been uploaded. New York City demographic data was sourced from the NYC 2010 census data (<https://www1.nyc.gov/site/planning/planning-level/nyc-population/census-2010.page>). Numbers of confirmed COVID-19 cases and mortalities were sourced from the NYC COVID-19 page (<https://www1.nyc.gov/site/doh/covid/covid-19-data.page>).

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**Author contributions** FK, VS, HvB and EMS conceived and designed the study. HvB wrote and maintained the IRB protocol. DS, CC and KJ performed the serological assays. JT, MMH, SF, KT, JJ, MDN and EMS collected, organized and aliquoted plasma samples. FA, CT, GAA and MM produced and purified recombinant proteins used in the ELISAs, and the positive control monoclonal antibody used in the assay. DS, VS, EMS, HvB and FK collected and analyzed the data. DS, VS and FK wrote the manuscript. All authors edited and approved the manuscript.

**Competing interests** Mount Sinai has licensed serological assays to commercial entities and has filed for patent protection for serological assays. DS, FA, VS and FK are listed as inventors on the pending patent application. CC, KJ, JT, MMH, MM, GAA, SF, KT, JJ, MDN, EMS, HvB, CT have no conflict of interest to declare.

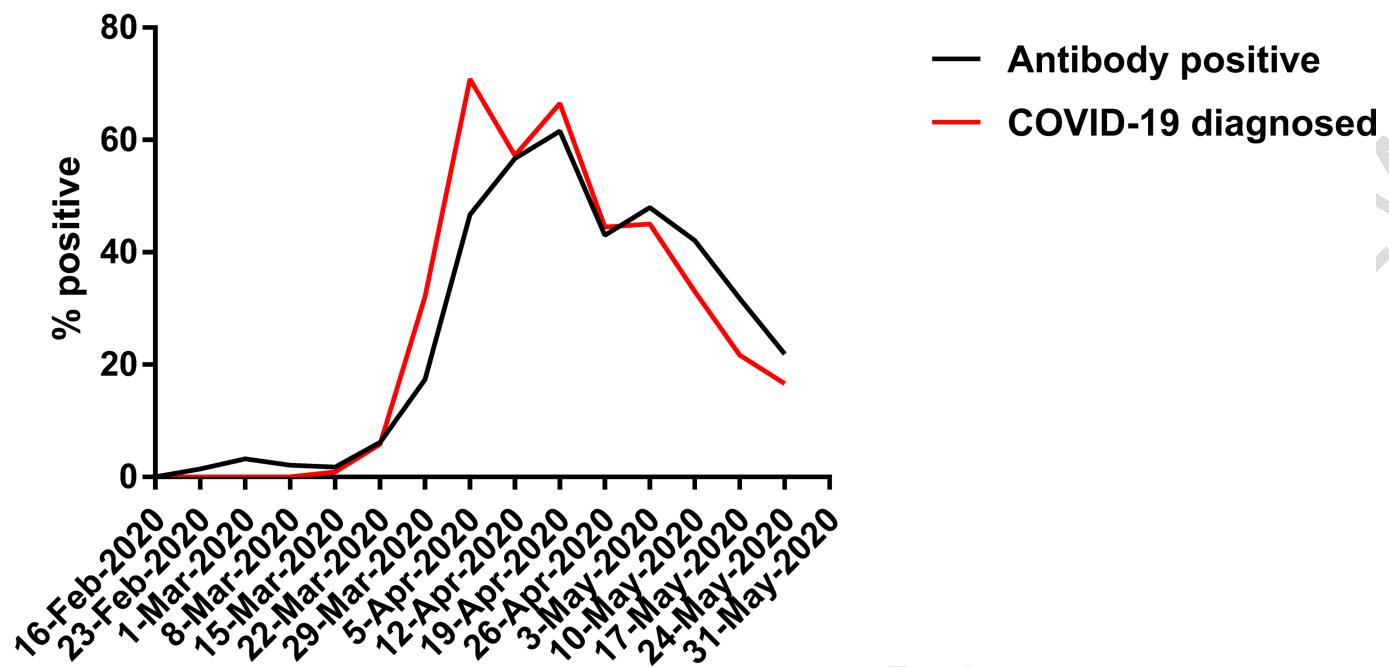
## Additional information

**Supplementary information** is available for this paper at <https://doi.org/10.1038/s41586-020-2912-6>.

**Correspondence and requests for materials** should be addressed to V.S., E.M.S., H.v.B. or F.K. **Peer review information** *Nature* thanks the anonymous reviewers for their contribution to the peer review of this work.

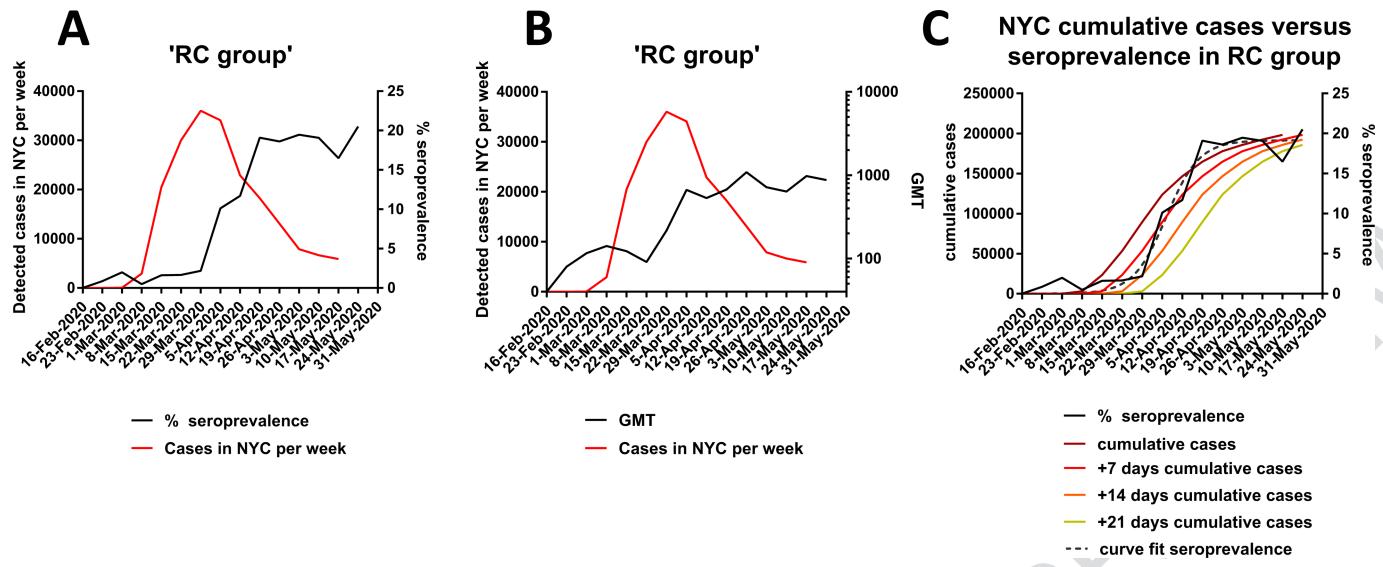
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## 'Urgent care group'



Extended Data Fig. 1 | Percent seroprevalence and percent COVID-19 diagnosed cases in the UC group per week over the observation period.

# Article



**Extended Data Fig. 2 | Antibody titers and increase of seroprevalence in the RC group in relationship to confirmed cases in NYC.** (A) Percent seroprevalence in the RC group versus detected cases in NYC per week over the observation period. (B) Geometric mean antibody titers (GMT) of positives in the RC group versus detected cases in NYC per week over the observation

period. (C) Increase of seroprevalence compared to cumulative case curves and cumulative case curves with 7, 14 or 21 day delays. Data for confirmed cases in NYC was retrieved from <https://www1.nyc.gov/site/doh/covid/covid-19-data.page>.

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**Extended Data Table 1 | Two-by-two contingency table to calculate sensitivity and specificity of SARS-CoV-2 antibody test**

Two-by-two contingency table to calculate sensitivity and specificity of SARS-CoV-2 antibody test

		COVID19		
		positive	negative	total
Test	positive	38	0	38
	negative	2	74	76
	total	40	74	114

	Value	95% CI
Sensitivity	0.95	0.835 to 0.9911
Specificity	1	0.9507 to 1
Positive Predictive Value	1	0.9082 to 1
Negative Predictive Value	0.9737	0.909 to 0.9953

\*Wilson/Brown test to compute CIs

# Article

**Extended Data Table 2 | Detailed sample numbers and seroprevalence per week for the RC group**

Week ending on	n	Female	Antibody positive	COVID-19 diagnosis
<b>OB/GYN</b>				
16-Feb-20	3	0 (0%)	0 (0%)	0 (0%)
23-Feb-20	175	159 (90.1%)	0 (0%)	0 (0%)
1-Mar-20	146	129 (88.4%)	1 (0.7%)	0 (0%)
8-Mar-20	143	132 (92.3%)	0 (0%)	0 (0%)
15-Mar-20	160	154 (96.3%)	4 (2.5%)	0 (0%)
22-Mar-20	161	151 (93.8%)	3 (1.9%)	0 (0%)
29-Mar-20	177	164 (92.7%)	5 (2.8%)	2 (1.1%)
5-Apr-20	167	154 (92.2%)	16 (9.6%)	13 (7.8%)
12-Apr-20	96	95 (99.0%)	15 (15.6%)	10 (10.4%)
19-Apr-20	138	137 (99.3%)	37 (26.8%)	24 (17.4%)
26-Apr-20	119	117 (98.3%)	29 (24.4%)	16 (13.5%)
3-May-20	125	125 (100%)	32 (25.6%)	26 (20.8%)
10-May-20	110	110 (100%)	32 (29.1%)	33 (30.0%)
17-May-20	114	114 (100%)	22 (19.3%)	32 (28.1%)
24-May-20	110	109 (99.1%)	27 (24.5%)	25 (22.7%)
31-May-20	111	111 (100%)	24 (21.6%)	36 (32.4%)
7-Jun-20	113	113 (100%)	12 (10.6%)	38 (33.6%)
14-Jun-20	118	118 (100%)	23 (19.5%)	24 (20.3%)
21-Jun-20	117	117 (100%)	25 (21.4%)	13 (11.1%)
28-Jun-20	123	123 (100%)	21 (17.1%)	10 (8.1%)
5-Jul-20	117	116 (99.2%)	26 (22.2%)	17 (14.5%)
<b>Oncology</b>				
16-Feb-20	0	N/A	N/A	N/A
23-Feb-20	166	78 (47%)	2 (1.2%)	0 (0%)
1-Mar-20	143	67 (46.9%)	3 (2.1%)	0 (0%)
8-Mar-20	151	71 (47.0%)	1 (0.7%)	0 (0%)
15-Mar-20	193	95 (49.2%)	3 (1.6%)	1 (0.5%)
22-Mar-20	166	84 (50.6%)	2 (1.2%)	1 (0.6%)
29-Mar-20	166	71 (42.8%)	3 (1.8%)	4 (2.4%)
5-Apr-20	128	53 (41.4%)	11 (8.6%)	6 (4.7%)
12-Apr-20	114	55 (48.3%)	9 (7.9%)	10 (8.8%)
19-Apr-20	91	40 (43.5%)	7 (7.7%)	12 (13.2%)
26-Apr-20	95	38 (40.0%)	13 (13.7%)	14 (14.7%)
3-May-20	107	51 (47.7%)	16 (15.0%)	15 (14.0%)
10-May-20	120	60 (50.0%)	15 (12.5%)	15 (12.5%)
17-May-20	123	58 (47.2%)	18 (14.6%)	15 (12.2%)
24-May-20	127	70 (55.1%)	22 (17.3%)	24 (18.9%)
31-May-20	125	68 (54.4%)	108 (13.6%)	18 (14.4%)
7-Jun-20	107	47 (43.9%)	90 (15.9%)	16 (15.0%)
14-Jun-20	114	54 (47.4%)	94 (17.5%)	20 (17.5%)
21-Jun-20	116	48 (41.4%)	96 (17.2%)	19 (16.4%)
28-Jun-20	119	40 (33.6%)	101 (15.1%)	17 (14.3%)
5-Jul-20	121	62 (51.2%)	98 (19.0%)	18 (14.9%)
<b>Surgery</b>				
16-Feb-20	7	5 (71.4%)	0 (0%)	0 (0%)
23-Feb-20	93	32 (34.4%)	2 (2.2%)	0 (0%)
1-Mar-20	90	53 (58.9%)	3 (3.3%)	0 (0%)
8-Mar-20	97	61 (62.9%)	1 (1.0%)	0 (0%)
15-Mar-20	108	60 (55.6%)	1 (0.9%)	0 (0%)
22-Mar-20	66	27 (41.0%)	1 (1.5%)	0 (0%)
29-Mar-20	44	15 (34.1%)	1 (2.3%)	4 (9.1%)
5-Apr-20	18	4 (22.2%)	5 (27.8%)	9 (50.0%)
12-Apr-20	12	4 (33.3%)	2 (16.7%)	3 (25.0%)
19-Apr-20	9	2 (22.2%)	1 (11.1%)	0 (0%)
26-Apr-20	4	1 (25.0%)	0 (0%)	0 (0%)
3-May-20	13	7 (53.9%)	0 (0%)	0 (0%)
10-May-20	43	20 (46.5%)	6 (14.0%)	2 (4.7%)
17-May-20	41	22 (53.7%)	6 (14.6%)	2 (4.9%)
24-May-20	68	35 (51.5%)	15 (22.1%)	5 (7.4%)
31-May-20	79	48 (60.8%)	17 (21.5%)	8 (13.1%)
7-Jun-20	54	29 (53.7%)	7 (13.0%)	2 (3.7%)
14-Jun-20	66	40 (60.6%)	13 (19.7%)	1 (1.5%)
21-Jun-20	36	19 (52.8%)	7 (19.4%)	3 (8.3%)
28-Jun-20	57	33 (57.9%)	10 (17.5%)	5 (8.8%)
5-Jul-20	67	32 (47.8%)	16 (23.9%)	3 (4.5%)
<b>Cardiology and other office visits</b>				
16-Feb-20	3	1 (33.3%)	0 (0%)	0 (0%)
23-Feb-20	26	12 (46.1%)	0 (0%)	0 (0%)
1-Mar-20	24	13 (54.2%)	1 (4.2%)	0 (0%)
8-Mar-20	16	8 (50.0%)	0 (0%)	0 (0%)
15-Mar-20	32	14 (43.8%)	0 (0%)	0 (0%)
22-Mar-20	32	13 (40.6%)	1 (3.1%)	0 (0%)
29-Mar-20	25	14 (56.0%)	0 (0%)	1 (4.0%)
5-Apr-20	13	9 (69.2%)	1 (7.7%)	2 (15.4%)
12-Apr-20	9	4 (44.4%)	1 (11.1%)	0 (0%)
19-Apr-20	3	3 (100%)	1 (33.3%)	1 (33.3%)
26-Apr-20	13	6 (46.2%)	1 (7.7%)	2 (15.4%)
3-May-20	17	6 (35.3%)	3 (17.6%)	1 (5.9%)
10-May-20	5	4 (80%)	0 (0%)	0 (0%)
17-May-20	7	5 (71.4%)	1 (14.3%)	1 (14.3%)
24-May-20	7	6 (86.7%)	0 (0%)	0 (0%)
31-May-20	7	3 (42.9%)	1 (14.3%)	1 (14.3%)
7-Jun-20	11	6 (54.5%)	2 (18.2%)	0 (0%)
14-Jun-20	11	6 (54.5%)	1 (9.1%)	0 (0%)
21-Jun-20	10	4 (40.0%)	3 (30.0%)	0 (0%)
28-Jun-20	6	2 (33.3%)	2 (33.3%)	0 (0%)
5-Jul-20	6	3 (50.0%)	4 (66.7%)	2 (33.3%)

**Extended Data Table 3 | Subtotal sample numbers and seroprevalence per week for RC and UC groups**

Week ending on	n	Female	Antibody positive	COVID-19 diagnosis
<b>Subtotal 'Routine care-group'</b>				
16-Feb-20	13	9 (69.2%)	0 (0%)	0 (0%)
23-Feb-20	460	281 (61.1%)	4 (0.9%)	0 (0%)
1-Mar-20	403	262 (65.0%)	8 (2.0%)	0 (0%)
8-Mar-20	407	272 (66.8%)	2 (0.5%)	0 (0%)
15-Mar-20	493	323 (65.5%)	8 (1.6%)	1 (0.2%)
22-Mar-20	425	275 (64.7%)	7 (1.7%)	1 (0.2%)
29-Mar-20	412	264 (64.1%)	9 (2.2%)	11 (2.7%)
5-Apr-20	326	220 (67.5%)	33 (10.1%)	30 (9.2%)
12-Apr-20	231	158 (68.4%)	27 (11.7%)	23 (10%)
19-Apr-20	241	182 (75.5%)	46 (19.1%)	37 (15.4%)
26-Apr-20	231	162 (70.1%)	43 (18.6%)	32 (13.9%)
3-May-20	262	189 (72.1%)	51 (19.5%)	42 (16.0%)
10-May-20	278	194 (69.8%)	53 (19.1%)	50 (18.0%)
17-May-20	285	199 (69.8%)	47 (16.5%)	50 (17.5%)
24-May-20	312	220 (70.5%)	64 (20.5%)	54 (17.3%)
31-May-20	322	230 (71.4%)	59 (18.3%)	63 (19.6%)
7-Jun-20	285	195 (68.4%)	38 (13.3%)	56 (19.7%)
14-Jun-20	309	218 (70.6%)	57 (18.4%)	45 (14.6%)
21-Jun-20	279	188 (67.4%)	55 (19.7%)	35 (12.5%)
28-Jun-20	305	198 (64.9%)	51 (16.7%)	32 (10.5%)
5-Jul-20	311	213 (68.5%)	69 (22.2%)	40 (12.9%)
<b>Emergency department and inpatient admissions ('Urgent care-group')</b>				
16-Feb-20	3	0 (0%)	0 (0%)	0 (0%)
23-Feb-20	213	95 (44.6%)	3 (1.4%)	0 (0%)
1-Mar-20	217	105 (48.4%)	7 (3.2%)	0 (0%)
8-Mar-20	238	99 (41.6%)	5 (2.1%)	0 (0%)
15-Mar-20	223	104 (46.6%)	4 (1.8%)	2 (0.9%)
22-Mar-20	243	95 (39.1%)	15 (6.2%)	14 (5.8%)
29-Mar-20	265	111 (41.9%)	46 (17.4%)	85 (32.1%)
5-Apr-20	274	108 (39.4%)	128 (46.7%)	194 (70.8%)
12-Apr-20	194	87 (44.9%)	110 (56.7%)	111 (57.2%)
19-Apr-20	203	100 (49.3%)	125 (61.6%)	135 (66.5%)
26-Apr-20	200	85 (42.5%)	86 (43.0%)	89 (44.5%)
3-May-20	198	89 (45.0%)	95 (48.0%)	89 (45.0%)
10-May-20	197	89 (45.2%)	83 (42.1%)	65 (33.0%)
17-May-20	189	92 (48.7%)	60 (31.7%)	41 (21.7%)
24-May-20	169	82 (48.5%)	38 (22.5%)	28 (16.6%)
31-May-20	171	93 (54.4%)	41 (24.0%)	26 (15.2%)
7-Jun-20	168	83 (49.4%)	43 (25.6%)	19 (11.3%)
14-Jun-20	174	79 (45.4%)	44 (25.3%)	19 (10.9%)
21-Jun-20	194	84 (43.3%)	49 (25.3%)	19 (9.8%)
28-Jun-20	186	90 (48.4%)	43 (23.1%)	14 (7.5%)
5-Jul-20	182	94 (51.6%)	42 (23.1%)	17 (9.3%)

Corresponding author(s): Florian Krammer

Last updated by author(s): Oct 9, 2020

## Reporting Summary

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- Estimates of effect sizes (e.g. Cohen's  $d$ , Pearson's  $r$ ), indicating how they were calculated

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### Software and code

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Data collection

Microsoft Excel (2016) was used to collect the data

Data analysis

Microsoft Excel (2016) and GraphPad Prism 8 were used to analyze data.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [guidelines for submitting code & software](#) for further information.

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# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	500 samples per week were chosen as a target sample size in the sampling period based on estimated availability of samples and capacity of the laboratory to handle and analyze samples. No specific sample-size calculations were performed.
Data exclusions	No data were excluded from analysis.
Replication	The sensitivity and specificity of the serological test used in this study have been established and are incorporated in the manuscript. Specimens have been tested once in the described two-step ELISA.
Randomization	To choose samples in a randomized and unbiased manner, plasma from up to the first 152 specimens for each location per collection week was then aliquoted for testing. All test samples were logged into a de-identified database and matched to anonymous patient identifiers and verified patient categories, after which duplicate samples obtained from the same patient within one week were retrospectively removed from further analysis.
Blinding	Operators performing the serological testing were blinded.

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems	Methods
n/a <input type="checkbox"/> Antibodies <input type="checkbox"/> Eukaryotic cell lines <input checked="" type="checkbox"/> Palaeontology <input checked="" type="checkbox"/> Animals and other organisms <input type="checkbox"/> Human research participants <input checked="" type="checkbox"/> Clinical data	n/a <input checked="" type="checkbox"/> Involved in the study <input checked="" type="checkbox"/> ChIP-seq <input checked="" type="checkbox"/> Flow cytometry <input checked="" type="checkbox"/> MRI-based neuroimaging

### Antibodies

Antibodies used	Anti-Human IgG (Fab specific)–Peroxidase antibody produced in goat (Sigma, #A0293)
Validation	Secondary antibodies obtained from Sigma-Aldrich were validated by the company and tested for specificity.

### Eukaryotic cell lines

Policy information about <a href="#">cell lines</a>	
Cell line source(s)	Expi293F mammalian suspension cells were obtained from Thermo Fisher.
Authentication	Cell lines were obtained from a commercial source. After receipt cells were recovered, passaged and not further authenticated.
Mycoplasma contamination	Cells tested negative for mycoplasma contamination.
Commonly misidentified lines (See <a href="#">ICLAC</a> register)	N/A

### Human research participants

Policy information about <a href="#">studies involving human research participants</a>	
Population characteristics	Specimens from subjects of all age groups (0-61+) were collected and tested. Subjects were separated in two different groups: Emergency department (44.3% female) and non-emergency department (67.2% female) visits.
Recruitment	Residual EDTA-anticoagulated blood specimens remaining after standard of care testing were obtained from the Mount Sinai Hospital Blood Bank and sorted by collection date, location, and by patient practice category (OB/GYN visits and deliveries; oncology visits; surgeries and related visits; Cardiology office/treatment visits; ED visits; and other related hospital admissions).

## Ethics oversight

This study (protocol HS# 20-00308) was reviewed by the Mount Sinai Health System Institutional Review Board, Icahn School of Medicine At Mount Sinai, and determined to be exempt human research as defined by Department of Health and Human Services (DHHS) regulations (45 CFR 46. 104). The collection and testing of residual plasma specimen was performed in a blinded manner, and all data used in this study was anonymized following local and reporting regulations through the use of an honest broker.

Note that full information on the approval of the study protocol must also be provided in the manuscript.