

41 Abstract

42 **Background:** Assessing the burden of COVID-19 based on medically-attended case counts is
43 suboptimal given its reliance on testing strategy, changing case definitions and the wide spectrum of
44 disease presentation. Population-based serosurveys provide one avenue for estimating infection rates
45 and monitoring the progression of the epidemic, overcoming many of these limitations.

46
47 **Methods:** Taking advantage of a pool of adult participants from population-representative surveys
48 conducted in Geneva, Switzerland, we implemented a study consisting of 8 weekly serosurveys among
49 these participants and their household members older than 5 years. We tested each participant for anti-
50 SARS-CoV-2-IgG antibodies using a commercially available enzyme-linked immunosorbent assay
51 (Euroimmun AG, Lübeck, Germany). We estimated seroprevalence using a Bayesian regression model
52 taking into account test performance and adjusting for the age and sex of Geneva's population.

53
54 **Results:** In the first three weeks, we enrolled 1335 participants coming from 633 households, with
55 16% <20 years of age and 53.6% female, a distribution similar to that of Geneva. In the first week, we
56 estimated a seroprevalence of 3.1% (95% CI 0.2-5.99, n=343). This increased to 6.1% (95% CI 2.6-
57 9.33, n=416) in the second, and to 9.7% (95% CI 6.1-13.11, n=576) in the third week. We found that
58 5-19 year-olds (6.0%, 95% CI 2.3-10.2%) had similar seroprevalence to 20-49 year olds (8.5%,
59 95%CI 4.99-11.7), while significantly lower seroprevalence was observed among those 50 and older
60 (3.7%, 95% CI 0.99-6.0, p=0.0008).

61
62 **Interpretation:** Assuming that the presence of IgG antibodies is at least in the short-term associated
63 with immunity, these results highlight that the epidemic is far from burning out simply due to herd
64 immunity. Further, no differences in seroprevalence between children and middle age adults are
65 observed. These results must be considered as Switzerland and the world look towards easing
66 restrictions aimed at curbing transmission.

67

68 Introduction

69 Although statistics on confirmed cases and deaths help in monitoring the dynamics of disease
70 propagation, estimates remain largely unreliable when trying to understand the proportion of the
71 population infected with SARS-CoV-2 for public health purposes ¹. For example, until recently most
72 European countries, including Switzerland, did not have sufficient nasopharyngeal swabs available for
73 RT-PCR screening of anyone suspected or at risk of infection with SARS-CoV-2. Generally,
74 asymptomatic individuals, including those in at-risk categories, are not screened. As a result, the
75 number of confirmed cases of SARS-CoV-2 infections is largely underestimated ². In this context,
76 seroprevalence surveys are of utmost importance for understanding the proportion of the population
77 that has already developed antibodies against the virus and is potentially protected towards a new
78 infection ³. As recommended by the World Health Organization (WHO), monitoring changes of
79 seroprevalence over time is also crucial at the beginning of an epidemic to anticipate and plan an
80 adequate public health response ⁴.

81

82 The canton of Geneva, Switzerland, reported its first confirmed COVID-19 case on February 26, with
83 5071 cases (10.15 per 1000 inhabitants) and 243 deaths as of April 30 ^{5,6}. As in most countries,
84 changing testing strategies over the course of the epidemics made it impossible to estimate the extent
85 of the population that had been infected, while this information is crucial to plan evidence-based
86 strategies to lift confinement measures. To assess the seroprevalence of anti-SARS-CoV-2 antibodies
87 in this area, we initiated a survey in a representative sample of the population ⁷. To do so, we
88 contacted subjects who already participated in the Bus Santé study (an annual health examination
89 survey of a representative sample of the population of the canton) ⁸ and invited them along with their
90 household members to participate to the SEROCov-POP seroprevalence survey ⁷. Here we present
91 results based on 1335 participants who took part to the study during the first 3 of 12 study weeks as
92 they are likely to inform public health policy makers in Europe and beyond.

93

94 Methods

95 Study Design

96 Each week, ~1300 randomly selected previous participants of the Bus Santé study with an email
97 address on file (n~10'072, **Figure S1**) were invited to participate in the SEROCov-POP study by
98 email, which provided a link to an online appointment booking system for a visit at one of two sites
99 within the proceeding seven days. Eligible participants with a non-valid email address were contacted
100 by phone to update their contact information. Since the third study week, each potential participant
101 that hadn't replied to the initial email invitation within 72h was reminded of the invitation by phone, in
102 order to increase participation rate. Potential participants then received a confirmation by email, which
103 included a link to a questionnaire and a consent form to complete at home and bring on the day of the
104 study visit. During the visit, study staff discussed the study once again with participants to ensure

informed consent. Participants were invited to bring all members of their household, aged 5 years and older, to join the SEROCO-V-POP study. An electronic validation system allowed participants to declare that they weren't in quarantine or isolation and didn't present with symptoms compatible with COVID-19 at the moment of making the appointment, in which case they were encouraged to book at a further date. Participants considered vulnerable according to the Swiss Federal Office of Public Health criteria ⁹ (over 65 years old, diabetic, suffering from cardio-vascular or respiratory disease, immunocompromised, suffering from active cancer or with a BMI > 35 kg/m²) were asked to contact us directly by phone or email to book an appointment on time slots reserved explicitly for this population, in order to reduce risk of exposure to the virus. Inclusion criteria included people aged 5 years and older, whose primary residence was in the canton of Geneva. Over the first 3 weeks, 31% of invited eligible participants took part in the study, 16% refused to participate, and 53% have a pending status (waiting for booking appointment, being recalled, etc). We collected 6 mL of peripheral venous blood from each adult participant and 3 mL from each child less than 14 years old. The SEROCO-V-POP study was approved by the Cantonal Research Ethics Commission of Geneva, Switzerland (CER16-363).

Laboratory Analyses

We assessed anti-SARS-CoV-2-IgG antibodies using a commercially available enzyme-linked immunosorbent assay (Euroimmun AG, Lübeck, Germany # EI 2606-9601 G) targeting the S1-domain of the spike protein of SARS-CoV-2; sera diluted 1:101 were processed on a EuroLabWorkstation ELISA. An in-house validation study, using a set of sera from 176 pre-pandemic negative controls and 181 RT-PCR confirmed COVID-19 cases was conducted to estimate test performance and optimal thresholds for definitive results ¹⁰. Based on this validation study, which set thresholds to maximize specificity and inter-assay variability in test classification, we considered those with OD/CI >= 1.5 to be positive. This threshold resulted in a sensitivity of 86.2% and a specificity of 100%. For these analyses we treated all indeterminate results (>0.5 OD/CI <1.5) as negatives (Figure S1).

Statistical Methods and Analyses

To estimate seroprevalence, we used a simple Bayesian regression model taking into account test performance, in addition to the age and sex of the population. In this framework, our goal is to estimate the true underlying seroprevalence, p , within the population:

$$x_i \sim \text{Bernoulli}(p_i \theta^+ + (1 - p_i) * (1 - \theta^-))$$

$$\text{logit}(p_i) = X\beta + \varepsilon_i$$

$$x^+ \sim \text{Binomial}(n^+, \theta^+)$$

$$x^- \sim \text{Binomial}(n^-, 1 - \theta^-)$$

$$\varepsilon_i \sim \text{Normal}(0, \sigma^2)$$

where x_i is the result of the IgG ELISA for the i th person ($i = 1, \dots, N$). The sensitivity, θ^+ , is determined using n^+ RT-PCR positive controls from the lab validation study, of which x^+ tested positive. The specificity, θ^- , is determined using n^- pre-pandemic negative controls, of which x^- tested positive. The probability of observing a diagnostic positive is a function of the true positive rate and the false negative rate with regards to the true underlying probability of seropositivity p_i . This probability itself is a function of covariates X , which consists of sex, age categories, and week of study, and their coefficients β as well as an error term, ϵ_i with variance σ^2 . We used naive priors on all parameters to allow for an exploration of the parameter space. We implemented this model in the Stan probabilistic programming language¹¹ and used the *rstan* package to run the model, analyse outputs. We ran 20,000 iterations with 4 chains and assessed convergence visually and using the R-hat statistic. While we did not account for household clustering specifically in this model, we developed a separate hierarchical model with a random intercept for household, including the modeling of test performance but with no covariates. We used this model to estimate the overall seroprevalence across the three weeks and compared to those from the model described above to understand the potential impact of not accounting for clustering within households.

To generate seroprevalence estimates adjusted to the age and sex distribution of the population, we sampled from the posterior for all age-sex strata proportional to the demographics in canton of Geneva. All estimates presented represent the mean of the posterior samples with the 2.5th and 97.5th percentiles of this distribution as the 95% confidence intervals (95%CI).

Results

In the first three weeks of the study starting on April 6, we enrolled a total of 1335 individuals in the SEROCov-POP survey (Figure S2). Included participants came from 633 different households, with 53.6% being female, and 16% being under 20 years of age (**Table 1**), displaying a similar distribution to that of the overall Geneva population¹². While 246 individuals participated alone to the study, 193 participants came with one other household member, 97 participants with two household members, and 97 participants with three or more household members.

In the first week, we estimated an overall seroprevalence of 3.1% (95% CI 0.2-5.9). This figure increased to 6.1% (95%CI 2.6-9.33, n=416) in the second week, and to 9.7% (95% CI 6.1-13.1, n=576) in the third week, mirroring the increase in confirmed cases in the weeks before the survey (**Figure 1**). While there were no meaningful differences in seroprevalence between men and women (**Table 1**), we found that 5-19 year olds (6.0%, 95% CI 2.3-10.2%) had a similar seroprevalence to 20-49 year olds (8.5%, 95% CI 4.9-11.7), whereas seroprevalence among those 50 and older (3.7%, 95% CI 0.9-6.0, p<0.01) was significantly lower.

As a sensitivity analysis, we estimated seroprevalence among the subset of participants who were originally enrolled in our previous representative surveys (**Table 2**). Within this subset, we observed similar seroprevalence as in the overall study population, with higher estimates in younger individuals (20-49 years vs. 50+ years), and with increasing seroprevalence estimates from the first to the third week of the study.

Discussion

The preliminary results of this study provide an important benchmark to assess the state of the epidemic. With an estimated 48'500 people having developed antibodies (9.7% of 500'000 inhabitants) while 4741 cases were confirmed on April 24th, we observe that there are roughly 10 infections for every COVID-19 confirmed case in Geneva, reflecting the variability in disease severity, testing practices and care-seeking behaviors. Further, we show that three weeks after the peak of confirmed cases, only 1 in 10 people has developed antibodies against SARS-CoV-2, even in one of the more heavily affected areas in Europe¹³. Thus, assuming that the presence of IgG antibodies measured in this study is at least in the short-term associated with immunity, these results highlight that the epidemic is far from burning out simply due to herd immunity. Given the time to development of IgG antibodies (1-3 weeks), we expect to continue seeing significant increases in seroprevalence over the coming weeks¹⁴.

We found no differences in seroprevalence between children/young-adults (5-19 years old) and middle age adults, with those older than 50 years having a significantly lower seroprevalence than 20-49 year olds. Although children present typical COVID-19 symptoms far less frequently than adults, these results provide support to emerging research showing that they indeed get infected at similar rates¹⁵. This should be considered in view of increased concerns about severe inflammatory syndromes in children that could be COVID-19-related¹⁶, and of the worldwide debate around opportunity and modality of school re-openings. While the sample size of older adults was small, the lower seroprevalence estimates in this group suggest that targeted efforts to reduce social mixing of elderly people with others may have succeeded. However, it remains possible that, because of an age-related compromised ability to generate adaptive immune responses, the elderly develop a lower IgG response after infection, something that needs further investigation¹⁷.

To our knowledge, this is the first study to perform a large-scale seroprevalence survey of anti-SARS-CoV-2 IgG antibodies where participants were selected from a representative sample of the general population. It is also unique in its repeated nature allowing the study of immunity dynamics in both adult and children populations. Our population-based design as well as the fact that we informed participants that individual results were not going to be disclosed until the end of the study, mitigate

selection bias. This study applies advanced statistical methods accounting for demographic structure and imperfect diagnostic test to estimate seroprevalence in the overall population while capturing uncertainty in the estimates.

Our study also has some important limitations to acknowledge. First, the primary analyses include randomly selected participants as well as members of their households, making this sample not entirely randomly selected. We attempt to adjust for some aspects of this through poststratification within our statistical model. Further, in sensitivity analyses we estimated the seroprevalence for just the original and found that it is similar to that of the full sample. Second, we were able to account for clustering within households only for overall prevalence pooling the three weeks, as there was not enough data to account for age, sex, and household clustering all together within this framework. The use of a random effects model to account for household clustering did not change pooled results. Finally, the recruitment of participants by email might exclude non tech-proficient individuals or people without access to technology; another survey specifically targeting vulnerable populations (socially and clinically) is ongoing.

Over the next weeks, we will continue monitoring weekly seroprevalence in the general population and will be able to provide more refined analysis on symptomatology and other socio-demographic data in relation to immunological status. Yet, a preliminary presentation of these results is deemed to be necessary to timely inform global policy makers on how to adapt planning of the next phases. Public sharing of our protocol can also help the global academic community to implement serosurveys in their areas. For at least one year, we will follow up participants via an online digital platform and repeated serological/RT-PCR testing in order to assess COVID19 incidence in the population. These longitudinal results will also inform us on the dynamics of immunity which remain debated at this stage.

Our results highlight that as hospitalizations have reduced in Geneva and other similar locations throughout the world, the immunologic landscape has not changed greatly since the onset of the pandemic, with the vast majority of people having no evidence of past infection. As the world develops plans to find a new balance between minimizing the direct impacts of COVID-19 on those infected and the indirect effects on all of society, serologic studies such as this are critical for providing new insights about transmission and the otherwise hidden immunologic state of the population.

253

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276

277 **Author's contribution**

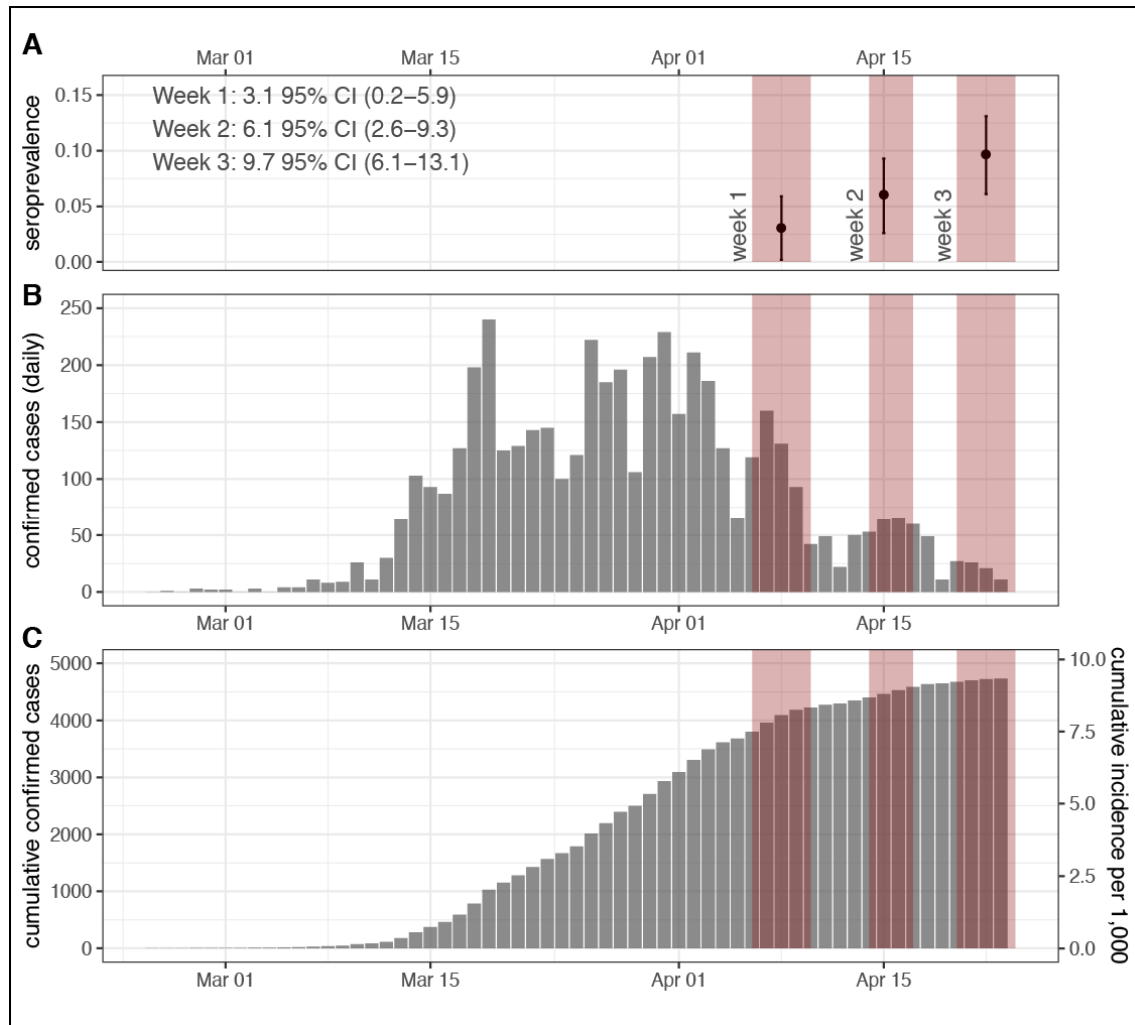
278 SS, AW, AF, LK and IG conceived the study. SS and IG drafted the first version of the manuscript.
 279 AA, AW, DP contributed to drafting sections of the manuscript. AA, SL and GP performed data
 280 analyses. SY, IAV, IE, NV, BM, LK performed lab analysis. GP, HB, AA, SL, DDR, DP, StS, KM,
 281 OK, SH, KPB, DT, DP, LG, FC participated in the study design and helped to draft the manuscript.
 282 All authors contributed to the interpretation of data, and read and approved the final manuscript.

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284 **Conflicts of interest to disclose**

285 No author had conflicts of interest to disclose.

Figure 1. Seroprevalence estimates and 95% confidence interval (CI)s for each week of the survey (A), daily confirmed cases reported in Geneva (B) and cumulative case counts per day and cumulative incidence rate of confirmed COVID-19 (C).



Red bars represent the periods where individuals were tested in each study week. IgG antibodies may take up to 3 weeks to develop.

292 **Table 1:** Overview of sample size and seroprevalence estimates by week, sex and age. Note that p-
 293 values are Bayesian p-values following Gelman et al.¹⁸.

	n	positive	seroprevalance	p-value
<i>Age</i>				
5-19	214	13 (6.1%)	6.0, 95% CI (2.3-10.2)	0.12
20-49	538	45 (8.4%)	8.5, 95% CI (4.9-11.7)	-
50+	583	25 (4.3%)	3.7, 95% CI (0.9-6.0)	<0.001
<i>Sex</i>				
Female	715	40 (5.6%)	5.6, 95% CI (3.1-8.1)	-
Male	620	43 (6.9%)	6.9, 95% CI (3.3-9.9)	0.24
<i>Week</i>				
Week 1	343	11 (3.2%)	3.1, 95% CI (0.2-5.9)	0.03
Week 2	416	22 (5.3%)	6.1, 95% CI (2.6-9.33)	-
Week 3	576	50 (8.7%)	9.7, 95% CI (6.1-13.1)	0.03

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Figure S1. Flow chart of inclusion in the study.

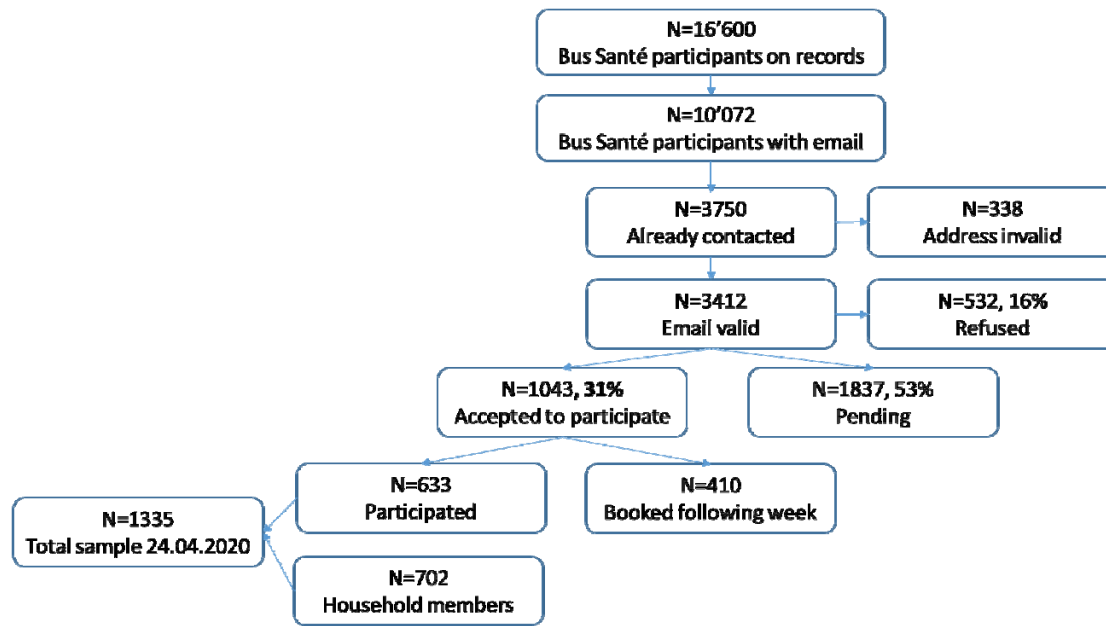
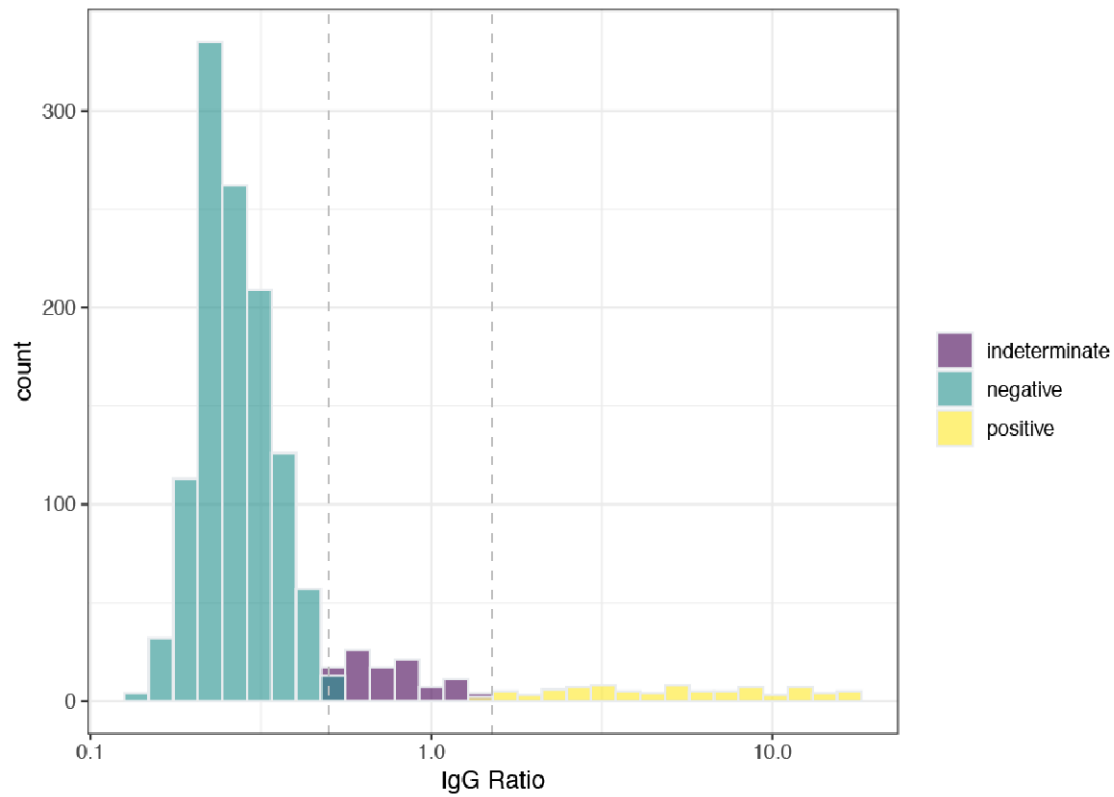


Table S1: Overview of sample size and seroprevalence estimates by week, sex and age (Bus Santé randomly selected participants only – other household members were excluded).

	n	positive	seroprevalance	p-value
<i>Age</i>				
20-49	253	2222 (8.7%)	9.5, 95% CI (5.3-14.0)	-
50+	375	15 (4.0%)	3.7, 95% CI (1.0-6.4)	0.00
<i>Sex</i>				
Female	340	1616 (4.7%)	5.7, 95% CI (2.8-9.1)	-
Male	288	21 (7.3%)	8.0, 95% CI (3.7-12.5)	0.19
<i>Week</i>				
Week 1	156	4 (2.6%)	3.0, 95% CI (0.1-7.2)	0.02
Week 2	190	12 (6.3%)	8.3, 95% CI (4.1-13.4)	-
Week 3	282	21 (7.4%)	9.0, 95% CI (4.5-13.7)	0.39

303 **Figure S2.** Density of ELISA ratios for all participants colored by result interpretation. All
 304 indeterminates were considered negative for these analyses.



References

- 1 Roda WC, Varughese MB, Han D, Li MY. Why is it difficult to accurately predict the COVID-19 epidemic? *Infectious Disease Modelling* 2020.
- 2 Verity R, Okell LC, Dorigatti I, *et al.* Estimates of the severity of coronavirus disease 2019: a model-based analysis. *The Lancet Infectious Diseases* 2020.
- 3 Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of Covid-19—studies needed. *New England Journal of Medicine* 2020; **382**: 1194–1196.
- 4 World Health Organization. Population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection. *Version* 2020; **1**: 17.
- 5 Office Fédéral de la Santé Publique. Rapport sur la situation épidémiologique en Suisse et dans la Principauté de Liechtenstein. 2020; published online April 30.
<https://www.bag.admin.ch/bag/fr/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/situation-schweiz-und-international.html#1164290551> (accessed April 30, 2020).
- 6 République et canton de Genève. COVID-19: Situation épidémiologique à Genève. GE.CH – République et canton de Genève. 2020; published online April 29.
<https://www.ge.ch/document/covid-19-situation-epidemiologique-geneve> (accessed April 30, 2020).
- 7 Primary Care Division-Geneva University Hospitals H. Repeated seroprevalence survey of anti-SARS-CoV-2 IgG antibodies in the population of the canton of Geneva. Geneva, Switzerland, 2020
https://static1.squarespace.com/static/5e7dd8f02d3bc353fbb05121/t/5e887016c7fa18312c3e00fa/1585999900784/Protocole_SEROCOV-POP30.03.pdf.
- 8 Guessous I, Gaspoz J-M, Theler J-M, Wolff H. High prevalence of forgoing healthcare for economic reasons in Switzerland: a population-based study in a region with universal health insurance coverage. *Preventive medicine* 2012; **55**: 521–7.
- 9 Conseil fédéral. RS 818.101.24 Ordonnance 2 du 13 mars 2020 sur les mesures destinées à lutter contre le coronavirus (COVID-19) (Ordonnance 2 COVID-19).
<https://www.admin.ch/opc/fr/classified-compilation/20200744/index.html> (accessed April 30, 2020).
- 10 Meyer B, Torriani G, Yerly S, *et al.* Validation of a commercially available SARS-CoV-2 serological Immunoassay. Unpublished manuscript. .
- 11 Carpenter B, Gelman A, Hoffman MD, *et al.* Stan: A probabilistic programming language. *Journal of statistical software* 2017; **76**.
- 12 République et canton de Genève. Statistiques cantonales - République et canton de Genève-T 01.01.8.01: Population résidante selon l'origine, le sexe, le groupe d'âges et l'état matrimonial, depuis 2013. https://www.ge.ch/statistique/domaines/01/01_01/tableaux.asp#5 (accessed April 30, 2020).
- 13 WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 99. Geneva, Switzerland, 2020
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200428-sitrep-99-covid-19.pdf?sfvrsn=119fc381_2.

349 14 Huang AT, Garcia-Carreras B, Hitchings MD, *et al.* A systematic review of antibody mediated
350 immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody
351 responses with severity of disease. *medRxiv* 2020.

352 15 Bi Q, Wu Y, Mei S, *et al.* Epidemiology and transmission of COVID-19 in 391 cases and 1286 of
353 their close contacts in Shenzhen, China: a retrospective cohort study. *The Lancet Infectious*
354 *Diseases* 2020.

355 16 Jones VG, Mills M, Suarez D, *et al.* COVID-19 and Kawasaki disease: novel virus and novel case.
356 *Hospital Pediatrics* 2020; : hpeds-2020.

357 17 Pawelec G, Weng N. Can an effective SARS-CoV-2 vaccine be developed for the older
358 population? 2020.

359 18 Gelman A, Meng X-L, Stern H. Posterior predictive assessment of model fitness via realized
360 discrepancies. *Statistica sinica* 1996; : 733–60.

361