THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet* 2020; published online June 11. http://dx.doi.org/10.1016/S0140-6736(20)31304-0.

Appendix: Seroprevalence of anti-SARS-COV-2 IgG antibodies in a population-based sample from Geneva, Switzerland

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S1. Overview of Statistical Framework

In this paper, our goal is to estimate the true underlying seroprevalence of the population ≥ 5 years old as measured each week, w in the of the Canton of Geneva, denoted p^*_w $(w = 1, \ldots, W = 5).\backslash$

We start by estimating the probability that each person in the serosurvey is seropositive using a Bayesian logistic regression model that accounts for household clustering, the sensitivity and specificity of the ELISA assay, each individual's age and sex, as well as the week when they were sampled:

$$\begin{aligned} x_i &\sim Bernoulli(p_i\theta^+ + (1-p_i) * (1-\theta^-)) \\ logit(p_i) &= \alpha_h + \mathbf{X}_i\boldsymbol{\beta} \\ \alpha_h &\sim Normal(0, \sigma^2) \\ x^+ &\sim Binomial(n^+, \theta^+) \\ x^- &\sim Binomial(n^-, 1-\theta^-) \end{aligned}$$

where x_i is the result of the IgG ELISA (in primary analyses) for the ith person $(i = 1, \ldots, N = 2766)$ in the serosurvey. 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 model estimates of the sensitivity and specificity are shown in Table S1. 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 for that person. This probability itself is a function of covariates $\mathbf{X}$, which consists of sex, age categories, and week of study, and their coefficients $\boldsymbol{\beta}$, and a random effect for household, α_h $(h = 1, \ldots, H = 1339)$, with variance σ^2. We used naive priors on all parameters to allow for an exploration of the parameter space. The priors on the sensitivity and specificity were flat from 0 to 1, equivalent to $Uniform(0, 1)$ or $Beta(1, 1)$. We used weak $Normal(0, 1)$ priors for the logistic regression coefficients $\boldsymbol{\beta}$. The prior on the standard deviation of the household effect, σ, was flat from 0 to infinity (we tested a positive half-Normal and it did not affect estimates).

We implemented this model in the Stan probabilistic programming language and used the `rstan` package in R to run the model and analyse outputs. We ran 5,000 iterations (4 chains with 1,500 iterations each with 250 for warm-up) and assessed convergence visually and using the R-hat statistic.[1,2]

S1.1. Estimation of weekly seroprevalence

We estimated the weekly seroprevalence p^*_w by post-stratifying the posterior samples of our parameter estimates to match the demographics of the Canton of Geneva at large. For every combination of age category $(a = 1, \ldots, A = 5)$, sex $(s = 0, 1)$, and week of sample, we estimated the probability of seropositivity, $p_{a,s,w}$

Table S1: The mean estimated sensitivity and specificity of the main model (EuroImmune) and for the primary and sensitivity analyses based on validation data from 181 positive controls and 176 negative pre-pandemic controls. EuroImmune is the EuroImmune IgG test with the manufacturers suggested cutoff. Geneva is using the EuroImmune IgG test with the cut-off suggested by Meyer et al. rIFA represents the use of EuroImmune IgG and testing of all with an OD/CI ratio > 0.5 with a recombinant immunofluorescence assay.

Test	Unadj. True Positives	Unadj. False Positives	Sensitivity (95% CI)	Specificity (95% CI)
EuroImmune	154 (85.1%)	0	85.6% (80.4-90.2)	99.8% (99.2-100.0)
Geneva	143 (79.0%)	0	79.8% (73.8-85.2)	99.8% (99.3-100.0)
rIFA	161 (89.0%)	0	89.0% (84.3-93.0)	99.8% (99.3-100.0)

for each posterior draw of $\boldsymbol{\beta}$ and σ. We can find estimate the weekly seroprevalence by taking a weighted average of the $p_{a,s,w}$, where weights are determined by the demographic distribution of the Canton of Geneva:

$$p_{a,s,w} = \int_0^1 logit^{-1}(\mathbf{X}_{a,s,w}\boldsymbol{\beta} + \sigma * \Phi^{-1}(t))dt$$
$$p^*_w = \sum_{a=1}^{A}\sum_{s=0}^{1} \frac{pop_{a,s}p_{a,s,w}}{pop}$$

where $\Phi^{-1}(t)$ is the quantile function of a standard normal distribution, $pop_{a,s}$ is the population of each demographic "cell" and *pop* is the total population of the Canton of Geneva. We estimate the average probability of seropositivity for the population in each demographic cell by integrating across all values of a logit-normal distribution with the standard deviation defined by the household random effect σ. Due to the high degree of household clustering in this study, accounting for the household random effect is important, as using the mean alone will lead to an underestimate of the probability of seropositivity (in addition to falsely low variance). For example, in the reference group (age 20-49, female, week 2), using only the mean results in an estimated seroprevalence of 1.4%, while adjusting that estimate for the household random effect increases that estimate to 9.2%. Once we estimated the values of all cells, then we averaged over them for each week, weighting by the proportion of the population of Geneva in each cell.

In the analysis consisting of only Bus Santé participants, we post-stratify directly from the distributions of the $\boldsymbol{\beta}$ coefficients since there is no household random effect in that model.

S1.2. Estimation of relative risk

To estimate the relative risk for some categorical variable z relative to the reference group (20-49 years old for age; female for sex) we used the following set of equations for each posterior draw of parameters $\boldsymbol{\beta}$ and σ:

$$p_z = \int_0^1 logit^{-1}(\beta_0 + \beta_z + \sigma * \Phi^{-1}(t))dt$$
$$p_0 = \int_0^1 logit^{-1}(\beta_0 + \sigma * \Phi^{-1}(t))dt$$
$$RR_x = p_z/p_0.$$

We estimated the seroprevalence for the population in category z (p_z) by integrating across all values of a logit-normal distribution with the standard deviation defined by the household random effect σ. We then divided that quantity by the estimated seroprevalence for the reference category (p_0) to calculate the relative risk (RR_z)

In the analysis consisting of only Bus Santé participants without their household contacts, there is no

Table S2: Weekly estimates of seroprevalence for Bus Santé participants

Week	Obs	Test positive	Test negative	Indeterminate	Seroprevalence (95% CI)	p
1	154	4 (2.6%)	148 (96.1%)	2 (1.3%)	3.4 (1.1-7.0)	0.032
2	214	14 (6.5%)	199 (93.0%)	1 (0.5%)	8.3 (5.0-12.5)	–
3	282	25 (8.9%)	252 (89.4%)	5 (1.8%)	10.0 (6.2-14.6)	0.522
4	296	16 (5.4%)	275 (92.9%)	5 (1.7%)	6.1 (3.1-9.7)	0.326
5	388	39 (10.1%)	345 (88.9%)	4 (1.0%)	11.4 (7.6-15.5)	0.228

Table S3: Relative risks among Bus Santé participants

Type	Category	Obs	Test positive	Test negative	Indeterminate	Relative risk (95% CI)	p
Age	[20,50)	539	46 (8.5%)	484 (89.8%)	9 (1.7%)	–	–
Age	[50,65)	542	43 (7.9%)	496 (91.5%)	3 (0.6%)	0.91 (0.58-1.33)	0.580
Age	[65,105)	253	9 (3.6%)	239 (94.5%)	5 (2.0%)	0.42 (0.18-0.77)	0.004
Sex	Female	701	43 (6.1%)	654 (93.3%)	4 (0.6%)	–	–
Sex	Male	633	55 (8.7%)	565 (89.3%)	13 (2.1%)	1.33 (0.86-1.93)	0.199

random effect for household, and therefore no integration is necessary:

$$p_z^{bus} = logit^{-1}(\beta_0 + \beta_z)$$
$$p_0^{bus} = logit^{-1}(\beta_0)$$
$$RR_z^{bus} = p_z^{bus}/p_0^{bus}.$$

S1.3. Bus Santé Subset Results

As the Bus Santé participants represent a population originally selected in a representative manner, we estimated seroprevalence and relative risk of seropositivity for these participants alone, without their household members. The estimates of seroprevalence by week are presented in Table S2 with the relative risks by age and sex in Table S3.

S1.4. Intracluster coefficient estimation

The intracluster coefficient (ICC) is calculated as in Guo and Zhao:

$$ICC = \frac{\sigma}{\sigma + \pi^2/3}$$

where $\pi^2/3$ is the variance of the standard logistic distribution.[3]

S2. Alternative diagnostic thresholds/tests

To test the robustness of our estimates, we ran our model using two other thresholds for determining seropositivity.

Meyer et al. established a higher cutoff for the EuroImmune assay of 1.5 (as opposed to the manufacturer recommended 1.1) to determine seropositivity.[4] The weekly seroprevalence estimates using this threshold are presented in Table S4.

The same study established a lower cutoff of 0.5 for seronegativity and denoted any cases falling between 0.5 and 1.5 as 'indeterminate'. We retested all indeterminate and positive cases using recombinant immunofluorescence (rIFA), which is often considered a confirmatory test. At the time of analysis, all but 11

Table S4: Weekly seroprevalence estimates using an alternative ELISA positivity cut-off (1.5) as described in Meyer et al. 2020.

Week	Obs	Test positive	Test negative	Indeterminate	Seroprevalence (95% CI)	p
1	341	11 (3.2%)	308 (90.3%)	22 (6.5%)	4.9 (2.4-8.1)	0.060
2	469	25 (5.3%)	418 (89.1%)	26 (5.5%)	8.4 (5.8-11.5)	–
3	577	50 (8.7%)	461 (79.9%)	66 (11.4%)	9.5 (6.6-12.8)	0.580
4	604	33 (5.5%)	536 (88.7%)	35 (5.8%)	6.4 (4.0-9.2)	0.260
5	775	77 (9.9%)	621 (80.1%)	77 (9.9%)	10.8 (8.1-13.9)	0.215

had been retested with rIFA. For these 11 samples, we assigned them the outcomes from the Meyer cutoff (positive if greater than 1.5). The seroprevalence estimates using this algorithm are presented in Table S5. While the rIFA results were a bit lower than the original results, all of the credible intervals overlap in each week across all techniques.

Table S5: Weekly seroprevalence estimates using ELISA results for all individuals with OD/CI less than 0.5 and using rIFA results for all others.

Week	Obs	Test positive	Test negative	Indeterminate	Seroprevalence (95% CI)	p
1	341	12 (3.5%)	329 (96.5%)	0 (0.0%)	4.5 (2.3-7.5)	0.081
2	469	24 (5.1%)	445 (94.9%)	0 (0.0%)	7.5 (5.1-10.2)	–
3	577	54 (9.4%)	523 (90.6%)	0 (0.0%)	9.0 (6.3-12.2)	0.442
4	604	40 (6.6%)	564 (93.4%)	0 (0.0%)	7.0 (4.7-9.8)	0.744
5	775	77 (9.9%)	698 (90.1%)	0 (0.0%)	9.6 (7.1-12.4)	0.236

S3. Additional Results

S3.0.1. Ratio of confirmed cases to infections

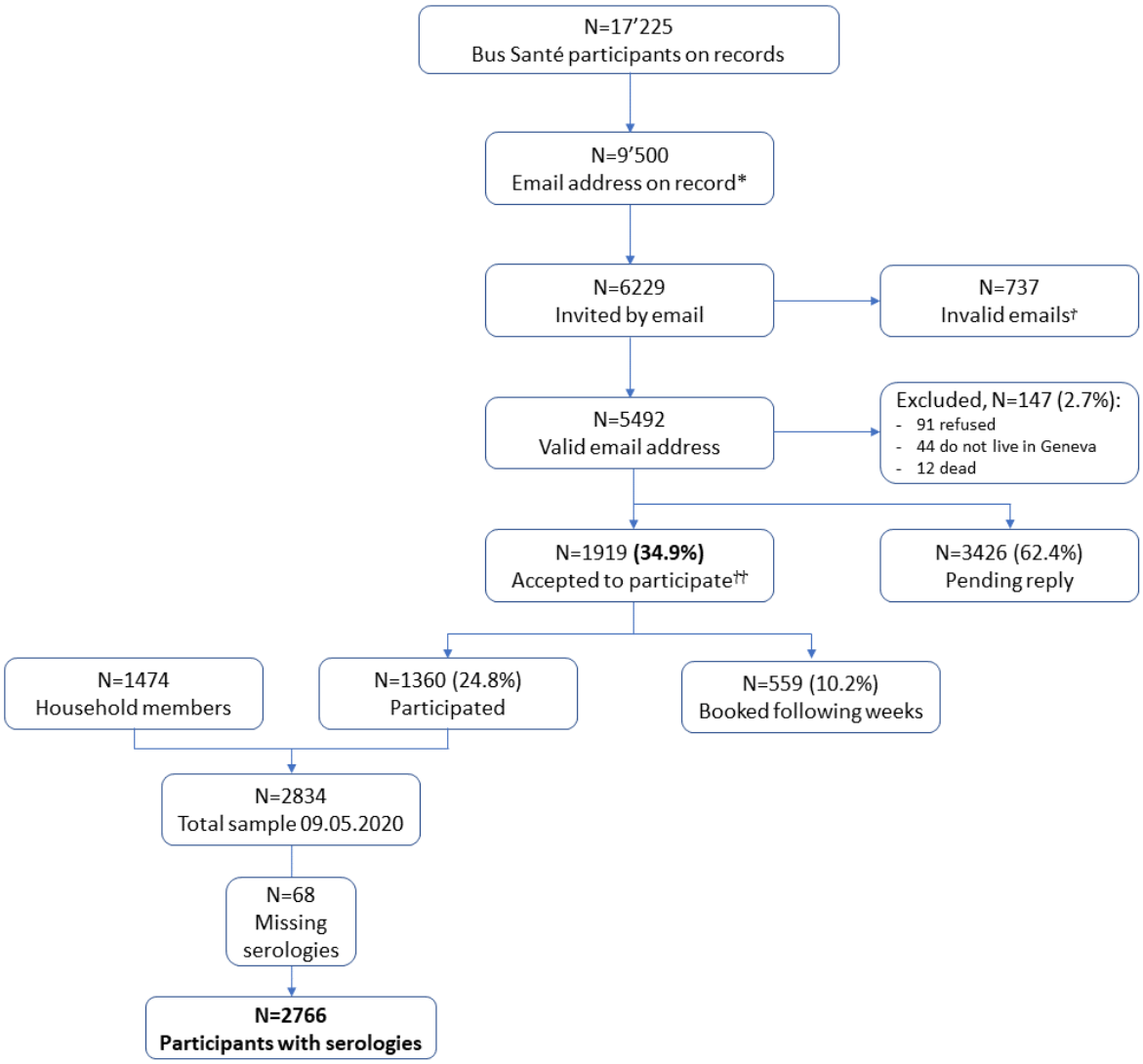
To estimate the ratio of implied infections (seroprevalence) to the number of clinically confirmed cases we used the daily number of confirmed COVID-19 cases from the Canton of Geneva (https://github.com/openZH/covid_19, data through 9-May-2020) and adjusted this time series by an assumed times from symptom onset to test result and from symptom onset to seroconversion.

We estimated the time from symptom onset to seroconversion using a parametric accelerated failure time model accounting for right censoring of observations using the `icenReg` package in R. We considered log-normal, Weibull and gamma distributions and selected the one with the highest log-likelihood. We found that a log-normal model fit the data best with a log-mean of 2.34 and a log-standard deviation of 0.38.

To estimate the time of seroconversion for each confirmed case, we first shift back the time series of confirmed cases (time of confirmation) by 6 days assuming this fixed lag across the population.[5] We then convoluted this time series with the time from symptom onset to seroconversion (truncated at 40 days). To calculate the ratio of implied infections to confirmed cases we then divide the implied number of infections by the sum the number of cases that have seroconverted until the mid-point of week 5 of the serosurvey (2020-05-06, 4727 out of a reported 5091 cases). We find that for every confirmed case we have 11.6 infections in the community.

References

1 Carpenter B, Gelman A, Hoffman MD *et al.* Stan: A Probabilistic Programming Language. *Journal of Statistical Software* 2017; **76**: 1–32.



*After inviting participants to update their contact information by postal mail or phone
† Participants with invalid emails are invited to update their email address by phone
†† Including 6 participants with no email address who were enrolled by phone

Figure S1: Flow chart of inclusion in the study.

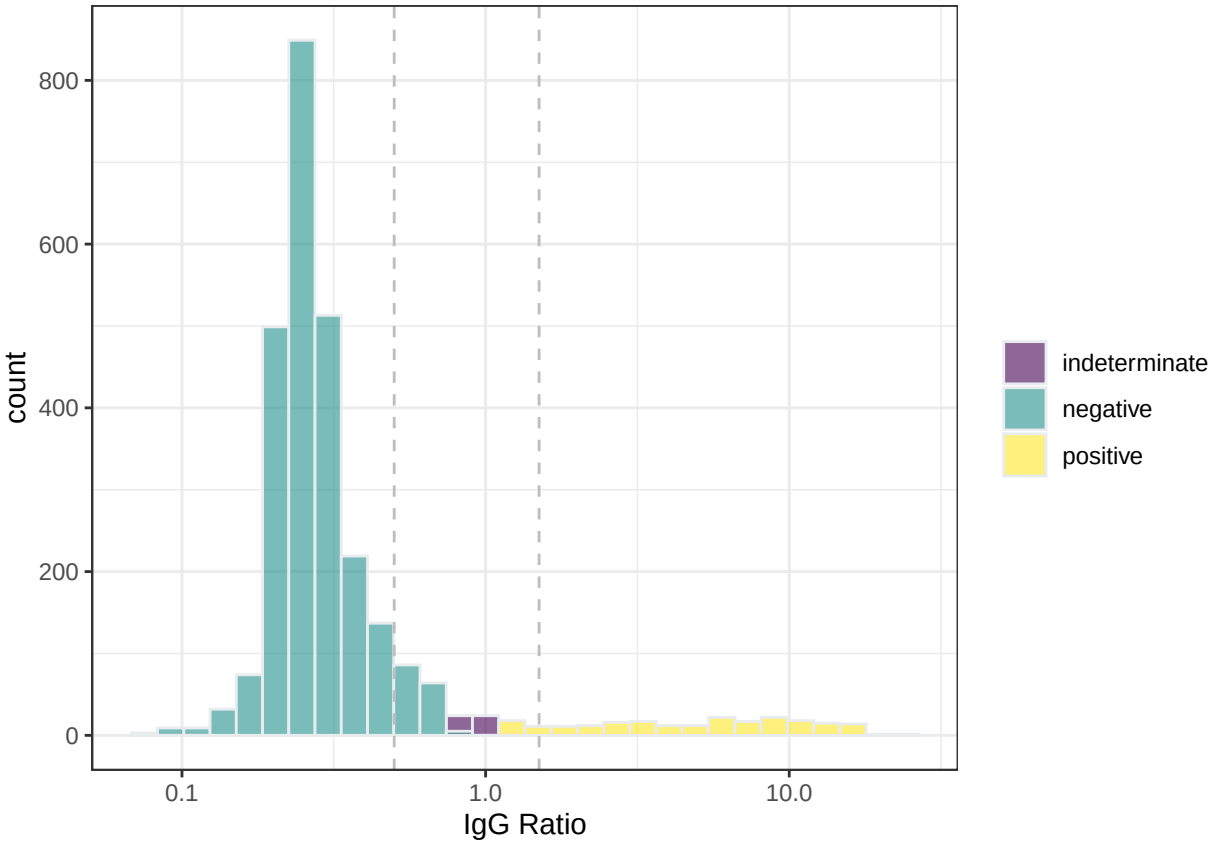


Figure S2: Histogram of IgG Ratios for the study 2,766 particpants. Colors represent manufacturer reccomended cutoffs of 0.8 and 1.1 for negative and positive.

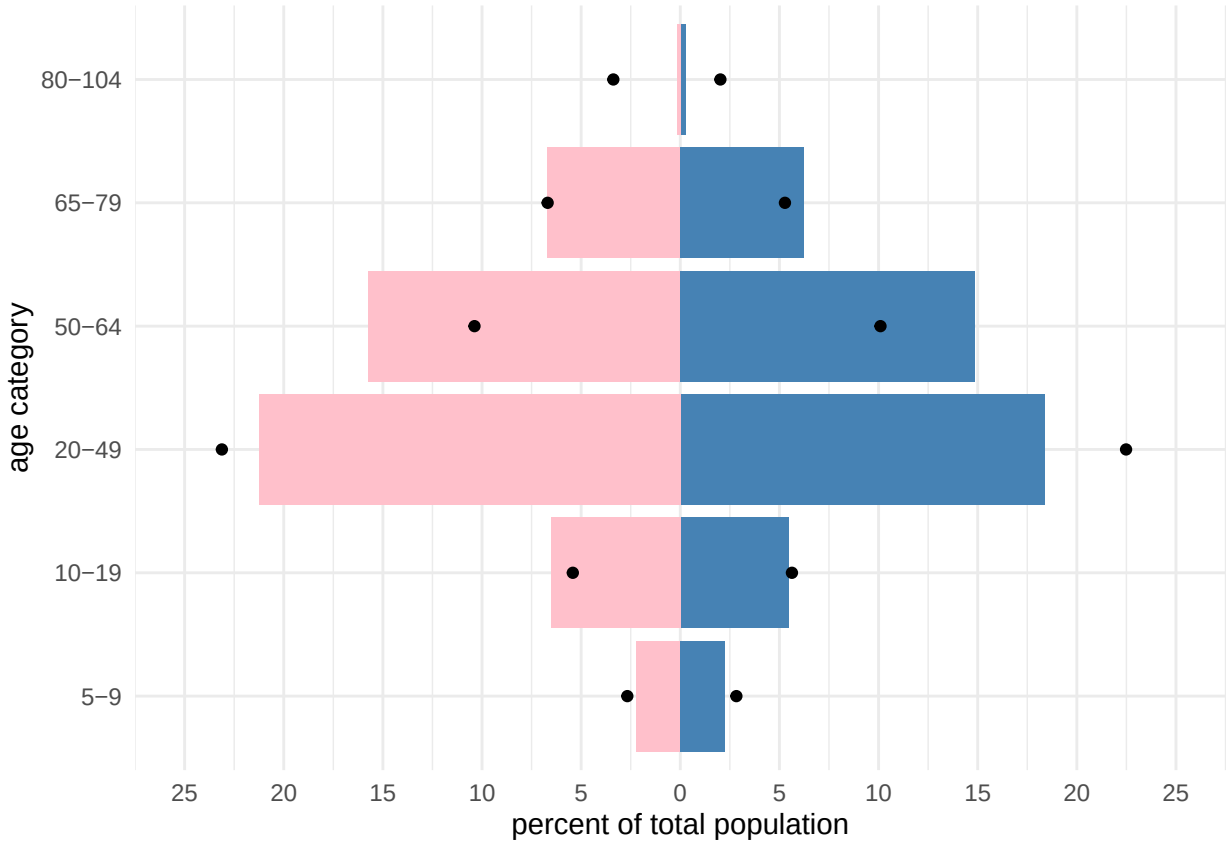


Figure S3: Comparison of age and sex of study population (bars) and the Geneva population (2019, dots). Blue represents males and pink represents females.

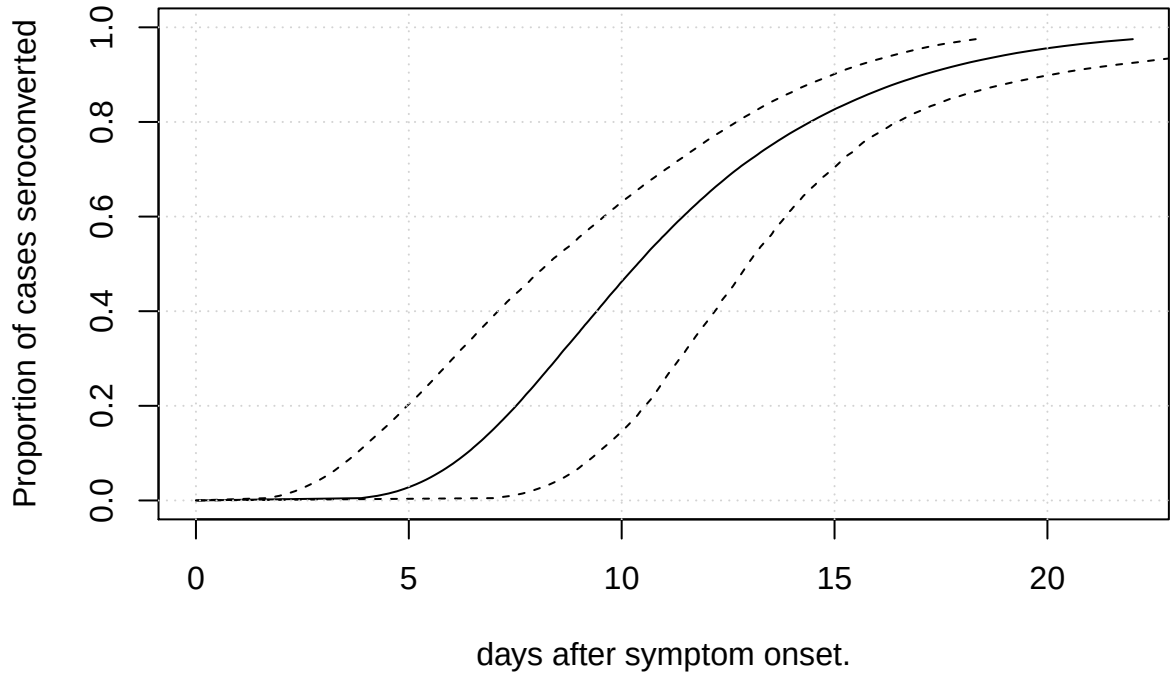


Figure S4: Estimated time to seroconversion after symptom onset assuming a log-normal distribution.

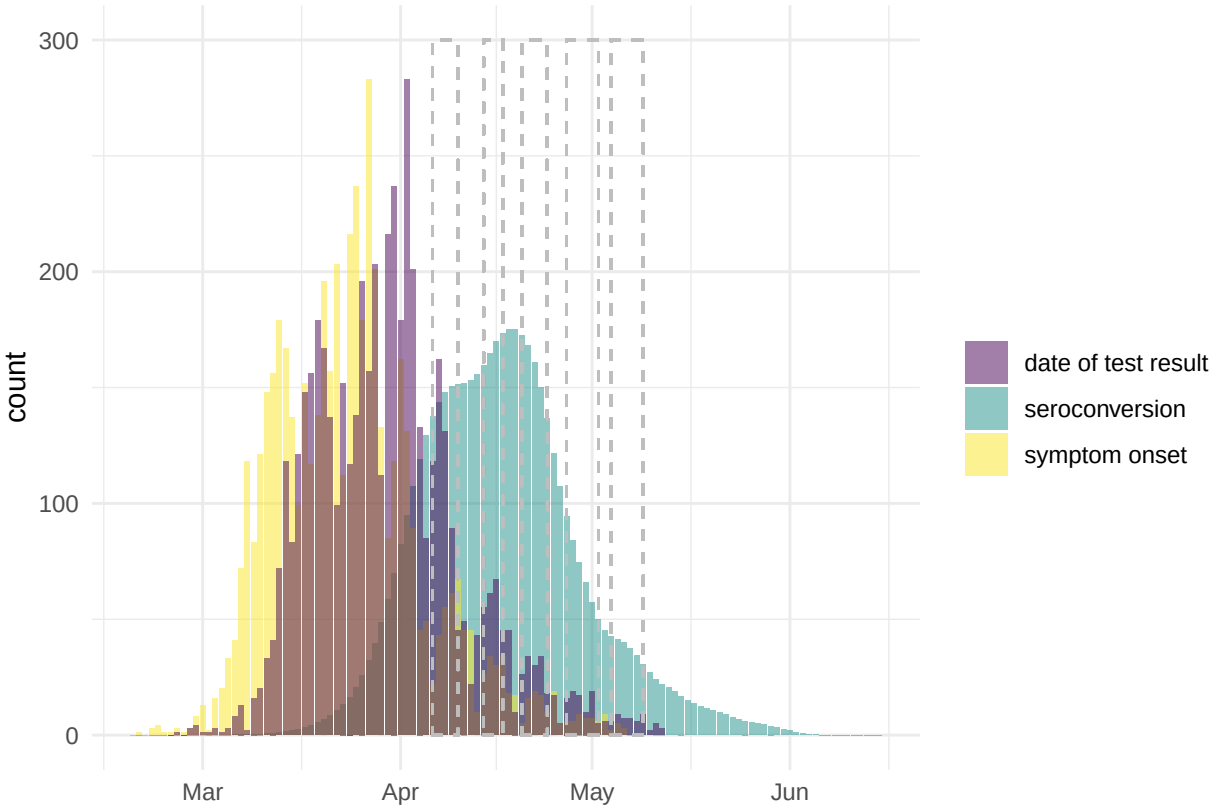


Figure S5: Time series of incident confirmed cases (purple), assumed times of symptom onsets (yellow) and times of seroconversion (green). Grey boxes represent time of each weekly serosurvey.

2 Stan Development Team. RStan: The R interface to Stan. 2018. http://mc-stan.org/.

3 Guo G, Zhao H. Multilevel Modeling for Binary Data. *Annual Review of Sociology* 2000; **26**: 441–62.

4 Meyer B, Torriani G, Yerly S *et al.* Validation of a commercially available SARS-CoV-2 serological Immunoassay. *medRxiv* 2020;: 2020.05.02.20080879.

5 Sciré J, Nadeau SA, Vaughan TG *et al.* Reproductive number of the COVID-19 epidemic in Switzerland with a focus on the Cantons of Basel-Stadt and Basel-Landschaft. *Swiss Medical Weekly* 2020; **150**: w20271.