Supplementary material

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### Supplementary information S1. Questions given to participants and used in present study, Specchio-COVID19 study

| Question                                                                 | Answer choices                        |
|-------------------------------------------------------------------------|---------------------------------------|
| What is your date of birth?                                             | day / month / year                     |
| What is your sex?                                                       | Male / Female / Intersex               |
| **Vaccination**                                                         |                                       |
| Have you received the first dose of the vaccine against COVID-19?        | Yes / No                               |
| If yes, date (day / month / year)                                       |                                       |
| Have you received the second dose of the vaccine against COVID-19?      | Yes / No                               |
| If yes, date (day / month / year)                                       |                                       |
| Since the beginning of the pandemic, have you had a confirmed COVID-19  | Yes / No                               |
| diagnosis, meaning having a positive COVID-19 from a nasal/throat swab, | If yes, date (day / month / year)      |
| either RT-PCR or rapid antigenic test?                                  |                                       |
| **Educational level**                                                   |                                       |
| What is the highest level diploma/certification that you have obtained?| None                                   |
|                                                                         | Primary school and/or orientation cycle|
|                                                                         | Secondary education – Maturité/High School|
|                                                                         | Professional training – Certified apprenticeship (CFC) |
|                                                                         | Professional training – Non-certified apprenticeship |
|                                                                         | Professional training – Higher professional degrees (post-CFC) |
|                                                                         | Tertiary education – Bachelor/Master degree |
|                                                                         | Tertiary education – Doctorate/PhD degree |
|                                                                         | Other                                  |
S1. Overview of Statistical Framework

Our aim was to infer the proportion of the population having any antibody against SARS-CoV-2, as well as the proportion of those who acquired antibodies through natural infection as opposed to vaccination. We do so by modelling jointly the antibody response measured by the Roche-N and Roche-S immunoassays together with participants’ responses to a vaccination questionnaire. We disentangle natural infection from vaccination antibody responses using the fact that the only available vaccines in Switzerland to date—the mRNA-1273 from Moderna/US NIAID,[5] and the mRNA-BNT162b2/Comirnaty from Pfizer/BioNTech[6]—both elicit a response exclusively to the S protein of SARS-CoV-2, as opposed to natural infections which typically elicit a response to both the N and S virus proteins. We expand previous Bayesian modelling frameworks used for seroprevalence estimates that account for demographic parameters (sex and age), test performance and household infection clustering,[1,2] The main additions to the previous models are that we now model jointly the response to both tests, and that we account for vaccination-induced antibody response.

S1.1 Multinomial response model

We model the Roche-S and Roche-N tests results for participant i, x_i, consisting of one of four possible outcome combinations \{n_{S+N}, n_{S-N}, n_{S+N}, n_{S-N}\} (+ indicates antibody presence; - indicates absence) with x_i \in \{[1, 0, 0, 0], [0, 1, 0, 0], [0, 0, 1, 0], [0, 0, 0, 1]\} using a multinomial distribution parametrized by parameter vector \pi_i = [\pi_{i+}, \pi_{i-}, \pi_{i++}, \pi_{i+-}] \in \mathbb{R}^4, where \pi_{im} is the probability of having Roche-S test result m and Roche-N result i, accounting both for the underlying probability of each antibody status p_{+/-}, and test sensitivity, \theta + and specificity, \theta -:

\[
x_i \sim \text{Multinomial}(\pi_i)
\]

\[
\pi_{i+} = \theta_2 \theta_{N} p_i^{+} + (1 - \theta_2) \theta_{N}^p p_i^{-} + \theta_2 (1 - \theta_{N}) p_i^{+} + (1 - \theta_2)(1 - \theta_{N}) p_i^{-},
\]

\[
\pi_{i-} = (1 - \theta_2) \theta_N p_i^{+} + \theta_2 \theta_N^p p_i^{-} + (1 - \theta_2)(1 - \theta_N) p_i^{+} + \theta_2 (1 - \theta_N) p_i^{-},
\]

\[
\pi_{i++} = \theta_2 (1 - \theta_N) p_i^{+} + (1 - \theta_2)(1 - \theta_N) p_i^{+} + \theta_2 \theta_N p_i^{-} + \theta_2 (1 - \theta_N) p_i^{-},
\]

\[
\pi_{i+-} = (1 - \theta_2)(1 - \theta_N) p_i^{+} + \theta_2 \theta_{N} p_i^{-} + \theta_2 (1 - \theta_N) p_i^{-} + \theta_2 (1 - \theta_N) p_i^{-}.
\]

The underlying probability of antibody status accounts both for the probability of natural infection \lambda_i and vaccination status, \nu_i \in \{0,1\}. Following previous modeling frameworks,[1,2] we model the probability of natural infection as a function of sex and age category, accounting for household infection clustering through a random effect, a_h:

\[
\text{logit}(\lambda_i) = \alpha_h + X_i \beta
\]

\[
a_h \sim \text{Normal}(0, \sigma^2_a)
\]

where \(X_i\) is the matrix of covariates, and \(\beta\) the vector of regression coefficients. The probabilities of antibody status are then given by:

\[
p_{i+} = \gamma_{+} \lambda_i + \gamma_{-} \nu_i
\]

\[
p_{i-} = \gamma_{-} \lambda_i (1 - \nu_i)
\]

\[
p_{i+} = (1 - \lambda_i) \nu_i + \gamma_{+} \lambda_i
\]

\[
p_{i-} = 1 - \nu_i (1 - \lambda_i) - \lambda_i,
\]

where \(\gamma_{+}, \gamma_{-}, \gamma_{+}\) are the conditional probability of having \(S^+N^+, S^-N^+, S^+N^-\) responses, respectively, upon natural infection, \(\nu_i\) is the probability of having a vaccine-induced \(S^+\) response as a function of the conditional probability of antibody response upon infection \(\eta_{i}, \nu_i = \eta_i \times \nu_i\).

S1.2 Vaccination

To obtain population-level seroprevalence estimates, we also model the proportion of vaccinated individuals in each sex/age class following the approach used for natural infection:

\[
v_i \sim \text{Bernoulli}(\phi_i)
\]
logit(\(\phi_i\)) = \(\alpha_{v,h} + X_i\beta_v\)

\(\alpha_{v,h} \sim \text{Normal}(0,\sigma_v^2)\)

Given vaccination policy recommendations in the state of Geneva, previously infected individuals were discouraged from being vaccinated in the early phase of the vaccination campaign, thus making the probability of vaccination dependent on the infection status of the individual. We account for this dependence by modelling separately the probability of vaccination given the infection status and marginalizing out the infection status:

\[ P(\{\cdot\}|\Theta) = \text{Bernoulli}(\{\cdot\}|\phi_i^\cdot) \times \text{Bernoulli}(\{\cdot\}|\phi^\cdot_i)(1-\lambda), \]

logit(\(\phi_i^\cdot\)) = \(\alpha_{v,h} + X_i\beta_v\)

logit(\(\phi_i\)) = \(\alpha_{v,h} + X_i\beta_v + X_i\beta^*_v\)

\(\alpha_{v,h} \sim \text{Normal}(0,\sigma_v^2)\),

where \(\Theta\) is the vector of all model parameters, \(I_I \sim I\) indicates infection and non-infection, respectively, and \(\beta^*_v\) is the vector of regression coefficients giving the difference in probability of vaccination between infected and non-infected individuals.

When estimating the population-level seroprevalence, we account for the conditional probability of vaccination given non-infection, \(p_{v|\cdot}\), in the probability of a negative S and N response accounting for household vaccination clustering, \(p^-\), as:

\[ p_{s,k} = 1 - p_{v|\cdot-s,k} \times (1 - p_{l,s,k}) - p_{l,s,k}, \]

where \(s,k\) denote the sex and age categories, \(p_{v|\cdot-s,k} = \int_0^1 \Phi_{s,k}^{-1}(t) dt = \int_0^1 \beta_{v,s,k} X_{s,k} + \sigma_v \Phi^{-1}(t) dt\), with \(\Phi^{-1}(t)\) being the normal quantile function, and similarly, \(p_{l,s,k}\) is the probability of infection with \(p_{l,s,k} = \int_0^1 \Phi_{s,k}^{-1}(t) dt = \int_0^1 \beta_{l,s,k} X_{s,k} + \sigma \Phi^{-1}(t) dt\).

### S1.3 Diagnostic test performance

The individual performance of both N and S tests is incorporated hierarchically following Gelman & Carpenter\[7\]. The sensitivity, \(\theta^-\), is determined using \(n^+\) RT-PCR positive controls from a laboratory validation study\[8\], of which \(x^+\) tested positive. The specificity, \(\theta^+\), is determined using \(n^-\) pre-pandemic negative controls, of which \(x^-\) tested positive. For the Roche N test, these values are modulated by data in Ainsworth et al.\[9\]. For the Roche S test, the laboratory study data are modulated by those available on the Roche website (last accessed July 19, 2021).

### S1.4 Priors

We follow a similar setting of the priors on the tests’ sensitivity and specificity as Gelman & Carpenter\[7\]. For study \(j\), the specificity \(\theta^-_j\) and sensitivity \(\theta^+_j\) are drawn from normal distributions on the log odds scale:

logit(\(\theta^-_j\)) \sim \text{Normal}(\mu_{\theta^-},\sigma_{\theta^-})

logit(\(\theta^+_j\)) \sim \text{Normal}(\mu_{\theta^+},\sigma_{\theta^+}).

Hyperparameters \(\mu_z\) and \(\sigma_z\) for \(z \in (\theta^-,\theta^+)\) follow, on the logit scale, normal distributions \(\mu_z \sim \text{N}(4,2)\) and positive half-normals \(\sigma_z \sim \text{N}^+(0,1)\), respectively. These priors on test performance were identical for both the Roche S and Roche N tests.

We used standard normal \(\text{N}(0,1)\) priors for the logistic regression coefficients for infection \(\beta\). For coefficients of vaccination \(\beta_v\) and for coefficients of the difference in probability of vaccination between infected and non-infected individuals \(\beta^*_v\), we also used standard normal except for the youngest age group (ages 0-5 years and 6-11 years). For these two age groups, \(\beta_v \sim \text{N}(-10,0.01)\) to reflect the fact that there was almost no vaccination in these youngest age groups in Geneva at the time of the study (NB vaccination registration for those aged 12-15 years opened on June 16, 2021:}
https://www.ge.ch/en/getting-vaccinated-against-covid-19/covid-19-vaccination-campaign-geneva, last accessed July 20, 2021). Correspondingly, $\beta_0 \sim \mathcal{N}(0, 0.01)$ for these two age groups.

The priors for the means of the household random effects $\alpha_h$ and $\alpha_{h,n}$, followed standard normal, and for standard deviations of the household random effects $\sigma_h \sim \mathcal{N}^+(0, 2)$ and $\sigma_v \sim \mathcal{N}^+(0, 2)$. We use a Dirichlet prior on the conditional probability of having $S^N, S^-N^+$, $S^+N^-$ responses upon natural infection, $\gamma^{++}, \gamma^{+-}, \gamma^{-+}, \gamma^{-} \sim \text{Dir}(10, 1, 1)$, to highly favour production of both anti-S and anti-N antibodies upon infection. Finally, we put a strong prior on the conditional probability of antibody response after vaccination $\eta_i \sim \text{Beta}(10, 0.1)$.

**S1.5 Implementation**

The model was coded in the probabilistic programming language Stan[10] using the Rstan package [11]. R [12] version 4.1 was used for data analysis. Four chains were run with 1500 iterations each, 250 of which were warmup, to give a total of 5000 posterior samples. Convergence was assessed by checking that $\hat{R} \approx 1$, that the effective sample size was reasonable for all parameters, and visually using shinystan[13] diagnostics checks.
Supplementary Figure S1. Participants recruitment and inclusion into analytical sample

7701 index individuals invited to participate

- 165 letters returned
  - 36 moved away from Geneva
  - 58 ineligible

- 6568 Invited index new individuals (OFS)

- 1133 Invited index returning individuals (previous studies)
  - 1133 Invited index
    - 1133 Invited index
      - 1497 index participants (23.7% participation rate) + 1001 household members
      - 1 participant excluded due to missing serology data

- 860 index participants (78.0% participation rate)
  - 860 index participants
    - 3355 individuals included in main analysis

3355 individuals included in main analysis

- 2520 individuals included in education-stratified analysis

- 835 excluded individuals:
  - 697 aged <18 years
  - 138 lacked education data

- 5 letters returned
  - 3 deceased
  - 3 moved away from Geneva
  - 19 ineligible

- 19 ineligible
  - 1497 index participants (23.7% participation rate) + 1001 household members
  - 1 participant excluded due to missing serology data

165 letters returned
36 moved away from Geneva
58 ineligible
Supplementary Figure S2. Comparison of age and sex composition of study sample (bars) and the Geneva population (dots).

Dark yellow represents males; blue represents females.
Supplementary Figure S3. Quantitative values of Roche-S and Roche-N immunoassays results

Each dot represents one participant. S value units are U/mL. For Roche-S, any values <0.4 were coded as 0.1, and any >2500 were coded as 3000 for ease of viewing, as our lab results do not provide more detailed data. The upper histogram for Roche S is thus a histogram without these 2 extremes i.e. binned from 0.4 to 2500 U/mL.
Supplementary Figure S4. Antibodies response category and vaccination status

Number of participants in the four possible categories of the S and N tests. + indicates antibodies detected; - indicates antibodies not detected.
### Supplementary Table S1. Comparison of education level in sample population and Geneva population

| Education level | Geneva population No. (%) | Study sample No. (%) |
|-----------------|---------------------------|---------------------|
| Mandatory       | 98246 (26.6)              | 203 (8.1)           |
| Secondary       | 118125 (32.0)             | 818 (32.5)          |
| Tertiary        | 153334 (41.5)             | 1499 (59.5)         |

Geneva population data available from: [https://www.ge.ch/statistique/domaines/15/15_03/tableaux.asp#1](https://www.ge.ch/statistique/domaines/15/15_03/tableaux.asp#1)
Supplementary Table S2. Comparison of proportion vaccinated in sample population and Geneva population

| Age group, years | Study sample | Vaccine (self-reported) | Geneva population | Vaccine |
|-----------------|--------------|-------------------------|-------------------|---------|
|                 | Individuals N | Vaccinated N (%)        | Individuals N | Vaccinated N (%) |
| 0-9             | 328          | 0 (0)                   | 52912            | 13 (0.02) |
| 10-19           | 444          | 56 (12.6)               | 53165            | 7604 (14.3) |
| 20-29           | 306          | 131 (42.8)              | 65068            | 27492 (42.3) |
| 30-39           | 423          | 189 (44.7)              | 76120            | 37679 (49.5) |
| 40-49           | 558          | 312 (55.9)              | 76190            | 47030 (61.7) |
| 50-59           | 505          | 363 (71.9)              | 71485            | 49217 (68.9) |
| 60-69           | 304          | 241 (79.3)              | 46829            | 35281 (75.3) |
| 70-79           | 236          | 218 (92.4)              | 36581            | 30053 (82.2) |
| ≥80             | 81           | 75 (92.6)               | 25778            | 21338 (82.7) |

Data on individuals vaccinated with at least 1 dose in study sample up to 4 July, 2021, to match data on individuals vaccinated in the general population of Geneva with at least 1 dose up to July 4, 2021.

Geneva population data available from: [https://www.covid19.admin.ch/en/vaccination/persons/d/demography?geo=GE&demoSum=total&demoAge=minOne](https://www.covid19.admin.ch/en/vaccination/persons/d/demography?geo=GE&demoSum=total&demoAge=minOne)
Supplementary Table S3. Proportion of participants having received at least 1 dose of the COVID-19 vaccine more than 14 days before serological assessment.

|                        | Participants | Vaccinated, at least one dose |                 |                 |
|------------------------|--------------|--------------------------------|-----------------|-----------------|
|                        | N (%)        | Reported<sup>a</sup> N (%)    | Estimated<sup>b</sup> % (95% CrI) |                 |
| Total                  | 3355         | 1449 (43.2)                    | 44.9 (43.4-46.4) |                 |
| Sex                    |              |                                |                 |                 |
| Male                   | 1541         | 669 (43.4)                     | 43.4 (41.3-45.5) |                 |
| Female                 | 1812         | 780 (43.0)                     | 46.3 (44.5-48.1) |                 |
| Age, y                 |              |                                |                 |                 |
| 0-5                    | 150          | 0 (0.0)                        | 0.0 (0.0-0.0)    |                 |
| 6-11                   | 281          | 0 (0.0)                        | 0.0 (0.0-0.0)    |                 |
| 12-17                  | 266          | 5 (1.9)                        | 3.7 (1.9-6.2)    |                 |
| 18-24                  | 300          | 85 (28.3)                      | 28.6 (23.8-33.6) |                 |
| 25-34                  | 372          | 121 (32.5)                     | 35.6 (31.1-40.2) |                 |
| 35-49                  | 805          | 323 (40.1)                     | 40.9 (37.3-44.5) |                 |
| 50-64                  | 732          | 517 (70.6)                     | 70.1 (66.7-73.3) |                 |
| 65-74                  | 207          | 174 (84.1)                     | 81.5 (75.8-86.5) |                 |
| ≥75                    | 242          | 224 (92.6)                     | 90.0 (86.0-93.5) |                 |
| Education level<sup>c</sup> |             |                                |                 |                 |
| Primary                | 203          | 100 (49.3)                     | 51.5 (48.5-54.4) |                 |
| Secondary              | 818          | 393 (48.0)                     | 52.9 (46.8-58.8) |                 |
| Tertiary               | 1499         | 878 (58.6)                     | 56.0 (53.6-58.4) |                 |

<sup>a</sup> Self-reported having received at least one dose of any COVID-19 vaccine, more than 14 days before blood drawing.

<sup>b</sup> Estimated vaccinated proportion in population, reported as % and 95% credible interval, adjusted for test performance of both immunoassays and post-stratified to account for age distribution in the Geneva general population and for household clustering of infection and vaccination.

<sup>c</sup> Self-reported education level among participants aged ≥18 years (N = 2520).
## Supplementary Table S4. Comparison of seroprevalence of anti-SARS-CoV-2 antibodies naturally developed through infection by November-December 2020 and June-July 2021, Geneva, Switzerland

| Geneva population N | Seroprevalence of antibodies after infection % | Percent increase | Absolute increase % points | Absolute increase N |
|---------------------|-----------------------------------------------|------------------|----------------------------|---------------------|
| Total               | Nov-Dec 2020       | Jun-Jul 2021     |                             |                     |
| Male                | 246655            | 21.9             | 30.4                        | 39%                 | 8.5                 | 20966 |
| Female              | 262119            | 20.4             | 29.5                        | 45%                 | 9.1                 | 23853 |
| Age, y              |                    |                  |                             |                      |                     |
| 0-5                 | 30633             | 14.9             | 20.8                        | 40%                 | 5.9                 | 1807  |
| 6-11                | 32041             | 22.8             | 31.4                        | 38%                 | 8.6                 | 2756  |
| 12-17               | 31726             | 23.6             | 37.7                        | 60%                 | 14.1                | 4473  |
| 18-24               | 42162             | 25.4             | 41.8                        | 65%                 | 16.4                | 6915  |
| 25-34               | 73285             | 25.9             | 31.9                        | 23%                 | 6.0                 | 4397  |
| 35-49               | 115274            | 23.6             | 32.2                        | 36%                 | 8.6                 | 9914  |
| 50-64               | 99841             | 21.2             | 29.8                        | 41%                 | 8.6                 | 8586  |
| 65-74               | 40317             | 14.9             | 22.5                        | 51%                 | 7.6                 | 3064  |
| ≥75                 | 43495             | 9.3              | 16.2                        | 74%                 | 6.9                 | 3001  |

* Seroprevalence based on results from Roche N test only.

Percent increase calculated as: \(\frac{(\text{Jun-Jul seroprevalence} / \text{Nov-Dec seroprevalence}) - 1}{100}\).

Absolute increase calculated as: \(\text{Jun-Jul seroprevalence} - \text{Nov-Dec seroprevalence}\).

Absolute increase N calculated as: absolute increase % \times Geneva population

Seroprevalence estimates for November-December 2020 from previous seroprevalence study [2].

Data on Geneva population available from: [https://www.ge.ch/statistique/domaines/01/01_01/tableaux.asp#5](https://www.ge.ch/statistique/domaines/01/01_01/tableaux.asp#5)
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