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Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-score matched cohort study

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Summary: This matched cohort study nested in a representative sample of the general population, observed a 94% reduction in the hazard of being infected among SARS-CoV-2 seropositive participants, when compared to seronegative controls, >8 months after serology assessment.

Abstract

Background: Serological assays detecting anti-SARS-CoV-2 antibodies are being widely deployed in studies and clinical practice. However, the duration and effectiveness of the protection conferred by the immune response remains to be assessed in population-based samples. To estimate the incidence of newly acquired SARS-CoV-2 infections in seropositive individuals as compared to seronegative controls we conducted a retrospective longitudinal matched study.

Methods: A seroprevalence survey including a representative sample of the population was conducted in Geneva, Switzerland between April and June 2020, immediately after the first pandemic wave. Seropositive participants were matched one-to-two to seronegative controls, using a propensity-score including age, gender, immunodeficiency, BMI, smoking status and education level. Each individual was linked to a state-registry of SARS-CoV-2 infections. Our primary outcome was confirmed infections occurring from serological status assessment to the end of the second pandemic wave (January 2021).

Results: Among 8344 serosurvey participants, 498 seropositive individuals were selected and matched with 996 seronegative controls. After a mean follow-up of 35.6 (SD 3.2) weeks, 7 out of 498 (1.4%) seropositive subjects had a positive SARS-CoV-2 test, of whom 5 (1.0%) were classified as reinfections. In contrast, the infection rate was higher in seronegative individuals (15.5%, 154/996) during a similar follow-up period (mean 34.7 [SD 3.2] weeks), corresponding to a 94% (95%CI 86% to 98%, P<0.001) reduction in the hazard of having a positive SARS-CoV-2 test for seropositives.

3

Conclusions: Seroconversion after SARS-CoV-2 infection confers protection against reinfection lasting at least 8 months. These findings could help global health authorities establishing priority for vaccine allocation.

Key words: SARS-CoV-2; reinfection; COVID-19; antibody; protection

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection induces

seroconversion detectable in up to 99% of individuals 2 to 4 weeks following infection with

the magnitude of antibody response being influenced by the severity of the disease, timing for

testing and the diagnostic performance of immunoassay[1, 2]. Markers of cellular and

humoral immunity have been shown to last at least 6-8 months after infection[3, 4]. However,

the extent to which and how long these markers are related to protection against future

infections need to be better defined. Because of limited testing availability in the early phases

of the pandemic and because of asymptomatic infections, seroprevalence surveys gave the

best estimate of the infection's burden in early phases of pandemic, with rates of

seropositivity below 10% after the first wave in Switzerland and in the US[5, 6]. Although

over 154 million virologically-confirmed SARS-CoV-2 infections have been registered

worldwide to date (May 2021), reports of reinfection are scarce and often limited to mild

cases[7], suggesting that SARS-CoV-2 infection elicits protective immunity[8]. Few recent

studies among healthcare workers[9-11], care homes[12], national registries[13-15] and

laboratory de-identified datasets[16] reported low incidence of reinfection among

seropositive or previously infected participants. However, generalisation of their conclusions

to the general population is limited by sampling bias (e.g. selection of healthy young

participants), lack of control for confounding factors (e.g. no adjustment for comorbidities) or

low incidence of infections during the period of observation. To date, no longitudinal

assessment of reinfection upon positive serological status has been conducted in

representative population-based samples including seniors and comorbid participants.

As in many countries worldwide, in Geneva, Switzerland, the ongoing pandemic has been

characterized by two waves, the first reaching its peak in March 2020, the second in

November 2020 (Figure 1). In Geneva, the cumulative incidence of virologically confirmed

5

SARS-CoV-2 infections was one of the highest in Europe, with about 8'600 confirmed cases per 100'000 inhabitants, accounted from the beginning of the pandemic in February 2020 to mid-January 2021[17]. With the second wave having occurred 8 months after the first, we had the opportunity to explore the risk of reinfections in a setting with high community transmission. Here we describe the results of a retrospective cohort study among a population-based sample in Geneva, Switzerland, comparing the risk of virologically-confirmed SARS-CoV-2 infections between individuals with detectable SARS-CoV-2 antibodies after the first pandemic wave to those without.

Methods

Data sources

Seroprevalence survey: From April to June 2020, a representative random sample of adults aged 20 to 74 years old living in the canton of Geneva and who had already participated to an annual health examination survey, were invited to participate in a SARS-CoV-2 serosurvey (SEROCoV-POP). Eligible participants were contacted by email or phone and were invited to bring all their household members aged five years or older. Eight-thousand-three-hundred and forty-four subjects were recruited for an estimated seroprevalence of about 8%; details of sampling and recruitment have been previously described [5, 18].

Coronavirus disease 2019 (COVID-19) cases: From early in the pandemic (February 2020), the General Directorate of Health of Geneva has maintained a centralized registry of SARS-CoV-2 infections and COVID-19 related deaths of the canton. Virologically confirmed SARS-CoV-2 infection was defined by the presence of a positive reverse transcriptase polymerase chain reaction (RT-PCR) or antigenic rapid diagnostic test (Ag RDT) on naso- or oropharyngeal swab, regardless the presence or absence of symptoms. Communication of testing results and accompanying meta-data was mandatory for all public and private

6

laboratories of the canton. Subjects with multiple testing during the same infective episode (i.e., 90-day time frame after first positive test) were counted as unique cases. During the second pandemic wave, public health authorities recommended the Geneva population to be tested in presence of symptoms or close contact with positive cases and encouraged them with a free from charge policy. As of January 25, 2021, 43'835 cases and 683 deaths had been registered[17]. Data on testing (date and type of test, test result, indication for testing) and COVID-19-related death were extracted and linked on a secured database to each individual included in SEROCoV-POP, using name, sex and date of birth as identity variables for matching.

Study design and participants

We conducted a retrospective cohort study among subjects 12 years and older enrolled in SEROCoV-POP between April 3 and June 30, 2020. We excluded children 5 to 12 years old as they were unlikely to be tested to SARS-CoV-2, even if symptomatic, based on recommendations from the Swiss Federal Office of Public Health. We classified participants into two groups, according to their baseline antibody status. To limit imbalance in distribution of potential confounders, all seropositive participants were matched to two seronegative controls on baseline characteristics using a propensity score with a logit link function, using a nearest-neighbour distance[19, 20]. The propensity score model included variables previously identified as being associated with the risk of developing SARS-CoV-2 infection[21]: age, gender, smoking status (current smoker or e-cigarette user), obesity (body mass index, BMI ≥30 kg/m^2) and socioeconomic status. The latter was represented in our main analysis by the level of formal education on a three-level scale: lower (i.e. compulsory education) middle (i.e. secondary education) and higher (i.e. tertiary education). It was replaced by neighbourhood socioeconomic deprivation, as previously described[22], in one of our sensitivity analyses. Finally, we included self-declared immunodeficiency (i.e. reported

7

immune system weakness due to an ongoing disease and/or treatment) in the model, as this variable could potentially influence antibodies development, risk of infection and prolonged viral shedding.

Laboratory analysis

Seropositivity was defined in our primary analysis by the detection of anti-S1 domain of spike protein IgG antibodies using a two-step sequential strategy. Antibodies were first detected by a commercially available ELISA (Euroimmun, Lübeck, Germany #EI 2606-9601 G). All potentially indeterminate (IgG ratio for detection ≥0.5) and positive results were confirmed by a recombinant immunofluorescence assay (rIFA), as this technique was considered the reference method in the laboratory of virology of Geneva University Hospitals (WHO Swiss reference lab) at the time the seroprevalence survey took place. Details on the procedures have been previously described[23]. Additionally, results of ELISA were used independently in our sensitivity analyses, using the manufacturer recommended ratio cut-off for positivity of ≥1.1 (sensitivity 93%, specificity 99%) and an optimized cut-off of ≥2.5 yielding a specificity of 100% against rIFA[23].

SARS-CoV-2 infection was assessed in the laboratory of virology of Geneva University Hospitals by testing oropharyngeal or nasopharyngeal swabs by RT-PCR using the SARS-CoV-2 reagent kit for BD Max system (Becton, Dickinson and Co, US), the Cobas 6800 SARS CoV2 RT-PCR (Roche, Switzerland), the Xpert Xpress SARS-CoV-2 assay (Cepheid, US) and the TaqPath COVID-19 RT-PCR assay (Thermo Fisher Scientific). Furthermore, results of RT-PCR came from nine private Geneva laboratories licenced by the Swiss Agency for Therapeutic Products, but no details on the diagnostic kits were available. From September 2020 Ag RDT was also implemented as an alternative diagnostic tool in canton of Geneva. Two tests were available: Panbio Covid-19 Ag Rapid Test device (Abbott

8

Diagnostics, Jena, Germany) and Standard Q (SD Biosensor/Roche, Switzerland). Both demonstrated a sensitivity of ≥85% and a specificity of about 100% in an in-house validation study[24]. All SARS-CoV-2 virologic tests (RT-PCR and Ag RDT) were considered equivalent in these analyses.

Reinfection case classification

Because viral RNA can be detected by RT-PCR more than two months after initial infection[25], and because swabs collected during the first wave were not available for viral RNA sequencing, all seropositive participants having tested positive for SARS-CoV-2 during follow-up were clinically investigated. Two independent adjudicators with experience in clinical management of SARS-CoV-2 infected patients evaluated suspected cases via hospital electronic health records or phone interview with participants. Adjudication was based on clinical judgement and criteria included, when available, reason for testing, subject's illness history (including date of symptom onset) and the value and temporal evolution in RT-PCR cycle threshold (Ct). The purpose of this investigation was to differentiate clinical reinfections from protracted RNA detection. Cases of suspected reinfections were classified as *likely* or *unlikely.* Conflicts were resolved by a third person (PDF).

Outcomes

The primary outcome was a virologically confirmed SARS-CoV-2 infection during the study period, defined by the time between inclusion (date of blood sample collection for serology) and death or the end of the study (January 25, 2021), whichever occurred first. Secondary outcomes were the incidence of virologically confirmed SARS-CoV-2 infections, the test per person ratio and the proportion of positive tests.

9

Statistical analysis

We estimated the hazard ratio of having a virologically confirmed SARS-CoV-2 infection comparing those who were anti-S1 IgG seropositive and seronegative at baseline using survival analysis methods. We used the Kaplan-Meier estimator to estimate the survival functions for each group. We used a Cox's proportional hazard model with a frailty term for matched set to estimate the hazard ratio. We tested the assumption of proportional hazards using a test based on the Schoenfeld residuals. Protection conferred by seropositivity was estimated computing one minus the hazard ratio. Baseline characteristics, incidence of infections, test/person ratio and test positivity were compared using t-test or McNamar test, as appropriate. We considered two-sided p-values <0.05 to be statistically significant. A plot of the mean differences between variable was used to evaluate the covariate balance after the matching, with a difference of less than 0.1 considered to be acceptable (see Supplementary Figure 1). Consistency of results was assessed for our primary outcome by estimating the hazard ratios for the full unmatched sample, using a univariable and multivariable Cox-proportional hazard model. The same covariates used in the propensity score model were selected for the multivariable model. Additional sensitivity analyses were conducted changing the variables included in the propensity score, varying the definitions of seropositivity, as described above, and considering all suspected cases as reinfections. Statistical analyses were conducted with R, version 4.0.3.

Ethics

The investigation conforms to the principles outlined in the Declaration of Helsinki and was approved as an amendment by the local Ethical Committee (CCER 2020-00881). Written informed consent was obtained from all participants.

10

Results

Study population

From a total of 8344 individuals included in the April-June 2020 serosurvey, 514 aged 12-years-old and older had anti-S1 SARS-CoV-2 IgG antibodies. Sixteen individuals were excluded from the analysis because of missing covariate data in matching variables (e.g., smoking status, education level, immunodeficiency). The remaining 498 were matched to 996 seronegative controls (Figure 2). Baseline characteristics were similar between study groups (Table 1). About half of participants were women (51% in both groups), mean age was 46.6 years (SD 16.6) in seropositives and 47.3 years (SD 16.3) in seronegatives. Mean BMI was about 24 kg/m^2 and the distribution of comorbidities was similar between seropositive and seronegative groups, represented mostly by hypertension (9.6% and 9.0% respectively) and chronic pulmonary disease (3.8% and 4.8%). Immunodeficiency was declared by 1.8% of participants in both groups. Most seropositive (91%) and one third of seronegative participants (36.7%) reported at least one COVID-19-consistent symptom from January 2020 to study inclusion. The list of symptoms considered to be COVID-19-consisent is available in Table 1 footnotes.

Risk of reinfection

After study inclusion, participants were followed-up for a period of 35.6 (SD 3.2) and 34.7 (SD 3.2) weeks in seropositive and seronegative groups, respectively. The testing rate (i.e., tests per person) during study follow-up was slightly different between groups, being 1.39 (SD 0.70) and 1.52 (SD 0.87), respectively. Inversely, the proportion of positive tests (i.e. positive tests among all tests performed) was significantly lower in the seropositive group (2.4% versus 11%, P <0.001). The rate of testing was extremely low in both groups before

11

study inclusion, due to limited test availability during the early phases of the pandemic (Figure 1).

Among all seropositive individuals at study inclusion, seven (1.4%) had a subsequent positive RT-PCR testing for SARS-CoV-2. Five of them (1%) were classified as *likely* and two as *unlikely* reinfections by outcome adjudicators (see Supplementary Table 1) corresponding to an incidence of 0.3 (95%CI 0.1 to 0.7) per 1000 person-weeks. By contrast, the rate of confirmed SARS-CoV-2 infections was significantly higher in seronegative individuals (15.5%, 154/996) corresponding to an incidence rate of 4.8 (95%CI 4.6 to 6.2) per 1000 person-weeks (*P* value for difference <0.001). Over the study follow-up, seropositive individuals were 94% less likely to have a virologically confirmed SARS-CoV-2 infection, when compared to individuals with no detectable anti-SARS-CoV-2 antibodies at study inclusion (hazard ratio of 0.06, 95% CI 0.02 to 0.14, *P*<0.001) (Figure 3). Results were consistent in all sensitivity analyses presented in Table 2 and in Supplementary Table 3. A post-hoc subgroup analysis suggested higher risk of reinfection in subgroup of individuals ≥60 years old (HR 0.44, 95%CI 0.14 to 1.4) when compared to participants younger than 60 years old (HR 0.05, 95%CI 0.01 to 0.20). Subgroup analyses are reported in Supplementary Table 4. Characteristics of individuals with suspected reinfection are presented in Supplementary Table 1 and 2.

Discussion

This population-based study including seniors and comorbid participants indicates conclusive evidence that having detectable anti-S1 SARS-CoV-2 antibodies is associated with a 94% significant reduction in the hazard of having a positive SARS-CoV-2 virologic test, more than 8 months after initial serologic testing.

12

Comparable findings have been reported in published reports. In one prospective cohort of UK healthcare workers accounting 1265 seroconverted participants, 2 asymptomatic infections were detected after a 6-months follow-up (incidence rate ratio of 0.12, 95% CI 0.03-0.47)[9]. However, the sample only included healthy working-age participants and the study was conducted over a low incidence period (1.08 positive test every 10'000 days at risk in seronegative subjects, versus 6.8 in our study). Similarly, a retrospective analysis of above 130'000 RT-PCR-confirmed SARS-CoV-2 infections in Qatar, observed a rate of reinfection (i.e. positive RT-PCR result ≥45 days after first positive swab) of only 0.05%[13]. Pandemic evolution in this country was monophasic with an intense initial phase affecting mainly young workers and lower incidence of infections from August 2020. The same limitations characterized a subsequent analysis of seroconverted individuals within the Qatar population (only available in preprint form)[26] limiting generalisation of conclusion to the general population. As the risk of infection is closely tied to intensity of exposure, our study allows to overcome these limitations by sampling a representative sample of the population with a follow-up covering into a high incidence phase having occurred several months after serological assessment.

In a retrospective analysis of a de-identified data from commercial laboratories including over 3 million US individuals, seropositive individuals were less likely of being tested positive to SARS-CoV-2, starting from 30 days after serological testing[14], although follow-up was limited (median of <2 months) and results were unadjusted for confounders.

In a prospective population-level observational study including over 500'000 individuals in Denmark. The estimated protection conferred by a previous positive RT-PCR was 80.5% (95% CI 75.4% to 84.5%)[27]. However, using RT-PCR instead of serology to define index infection and the absence of verification of suspected reinfections may have underestimated protection. Finally, promising results have been reported for vaccines using lipid

13

nanoparticle-mRNA technology with protection rate above 90% after two injections after a median follow-up of 2 months[28, 29]. In the present study, similar or higher rate of protection was conferred by seroconversion and lasted for a mean period of over 8 months.

This study has some limitations. First, not all individuals included in SEROCoV-POP were randomly selected from the community, because original participants were invited to come with their household members. However, characteristics of participants were previously compared with participants of community-surveys in Geneva and did not differ significantly[5]. Second, it is important to consider that although the cantonal testing registry used for identifying infections is wide, the study is limited in being able to only account for infections for which a confirmatory test was performed. The number of positive tests depend on screening strategies enacted by health authorities and access to the tests. This may have caused under-detection, despite testing was broadly deployed during the second wave lowering the undetected/detected ratio from 11.6 during the first wave to 2.7 during the second[30]. That risk of underdetection may be greater in seropositive individuals assuming that reinfections are less symptomatic. Moreover, excessive under-testing during follow-up could potentially have occurred in seropositive individuals because of awareness of their serology result and may have influenced testing behaviour. However, this is not supported by the similar testing rate we observed in the two study groups and the low percentage of positivity in the seropositive group. Third, due to their low incidence during the study period, we cannot infer protection against new SARS-CoV-2 variants[31, 32]. In fact, by the end of follow-up, variants with a potential of immune escape were only anecdotally detected by the laboratory of virology of the Geneva University Hospitals. Finally, immunoassays could be a source of criticism because of their variable diagnostic performance leading to misclassification bias. In our study, accuracy of commercial serological assays was improved by systematic confirmation of results by rIFA or using a higher ELISA cut off in the

14

sensitivity analyses. It is worth noting that comparable results were obtained in sensitivity analyses using a less conservative strategy (i.e commercial ELISA without confirmation with manufacturer cut-offs for positivity).

Our study has also several strengths. First, serological status was determined for all individuals in the early phases of the pandemic allowing a uniform and relatively long longitudinal follow-up. Second, results were concordant across all sensitivity analyses raising robustness of our conclusions. Third, even if no viral RNA sequencing was available for comparison, every case of potential reinfection was identified and individually verified by two independent outcome adjudicators acceding to the complete available clinical information. Fourth, in contrast with most of the previously cited studies, our sample was composed by a large number of participants aged 60 years or more and included comorbid subjects. The risk of reinfection seems to be higher in participants ≥60 years old (HR 0.44, 95%CI 0.14 to 1.4, Supplementary Table 4). Due to the low number of reinfections, subgroup analyses must be interpreted with caution. It is however concordant with a large cohort study reporting a relative risk of 0.529 (0.372 to 0.753) among participants ≥65 years old versus 0.195 (95%CI 0.155 to 0.246) for the whole cohort[27].

In conclusion, documented SARS-CoV-2 reinfections were exceedingly rare, with an incidence of 0.3 infections for every 1000 persons-week, and none were severe. Seroconversion after symptomatic or asymptomatic SARS-CoV-2 infection seems to be associated with a 10-fold reduction in risk of successive viral infection contamination, lasting at least eight months. These findings are of utmost importance for global health authorities facing the challenge of efficiently and rapidly deploying mass vaccination with supply shortages at the same time as lifting the restrictions in place.

15

NOTES

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Potential conflicts of interest

D.C. reports consulting fees from Medela AG, outside the submitted work. All other authors declare that they have no conflicts to report.

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19

Table 1. Demographics and characteristics of the matched seropositive and seronegative individuals

	Seropositive (n=498)	Seronegative (n=996)	*P* Value
Age, years, mean (SD)	46.6 (16.6)	47.3 (16.3)	-
Age group, years, No. (%)			
12-19	32 (6.4)	61 (6.1)	
20-39	139 (28.0)	280 (28.1)	
40-59	231 (46.4)	462 (46.4)	
60-79	90 (18.1)	181 (18.2)	
≥ 80	6 (1.2)	12 (1.2)	
Female, No. (%)	256 (51.4)	510 (51.2)	-
BMI, kg/m^2, mean (SD)	23.8 (4.1)	23.7 (4.4)	-
Comorbidity, No. (%)			
Diabetes	12 (2.4)	27 (2.7)	-
Hypertension	48 (9.6)	96 (9.0)	-
Chronic pulmonary disease	19 (3.8)	48 (4.8)	-
Cancer	10 (2.0)	27 (2.7)	-
Immunodeficiency	9 (1.8)	18 (1.8)	-
Current smoker[s], No. (%)	66 (13.3)	134 (13.5)	-
Education, No. (%)			-
Lower education	40 (8.0)	77 (7.7)	
Middle education	190 (38.2)	381 (38.3)	
Higher education	268 (53.8)	538 (54.0)	
Follow-up, weeks, mean (SD)	35.6 (3.2)	34.7 (3.2)	<0.001
Self-reported symptoms before study inclusion, No. (%)			
Asymptomatic	44 (9)	631 (63.3)	<0.001
Symptomatic[a]	454 (91)	365 (36.7)	<0.001
Rate of testing after study inclusion, mean (SD), No. per individual	1.4 (0.7)	1.5 (0.9)	0.041
Proportion of positive test during follow-up[b], %	2.4 %	11 %	<0.001
Incidence of virologically confirmed SARS-CoV-2 infections, No. every 1000 person-week (95%CI)	0.3 (0.1 to 0.7)	4.8 (4.6 to 6.2)	<0.001

[a] Symptomatic individuals reported at least one COVID-19-related symptom (i.e. fever, cough, cold, throat pain, panting, headache, muscular or articular pain, fatigue, inappetence, nausea, diarrhea, stomach pain, taste and smell loss), from January 2020 to study inclusion. BMI means body mass index.

[b] Proportion of positive tests among all tests performed during follow-up. Individuals could have no or multiple testing. Tests refer either to RT-PCR or antigenic rapid diagnostic tests.

[c] Tobacco or e-cigarette users.

20

Table 2. Number and risk of infection in seropositive and seronegative study groups according to definition of seropositivity.

Immunoassay strategy	Number of infections, No. (%)		Hazard ratio (95%CI)	P value
	seropositive	seronegative		
Two-step strategy[a]	5/498 (1.0%)	154/996 (15.5%)	0.06 (0.02 to 0.14)	<0.001
EI only, manufacturer cut-off[b]	12/551 (2.2%)	200/1102 (18.2%)	0.11 (0.06 to 0.20)	<0.001
EI only, optimized cut-off[c]	3/381 (0.8%)	98/762 (12.8%)	0.05 (0.01 to 0.14)	<0.001

[a] Euroimmun ELISA IgG ratio ≥ 0.5 and subsequent confirmation with recombinant immunofluorescence assay

[b] Euroimmun ELISA IgG ratio ≥ 1.1 without confirmation

[c] Euroimmun ELISA IgG ratio ≥ 2.5 without confirmation

21

FIGURE LEGENDS

Figure 1. Incidence of testing and SARS-CoV-2 infections during first and second pandemic waves in the canton of Geneva (Switzerland). Panel a: weekly incidence of testing in the study sample; panel b: weekly incidence of testing in the Geneva population. Panel c: weekly incidence of SARS-CoV-2 infections; panel d: cumulative incidence of SARS-CoV-2 infections.

Figure 2. Study flow diagram

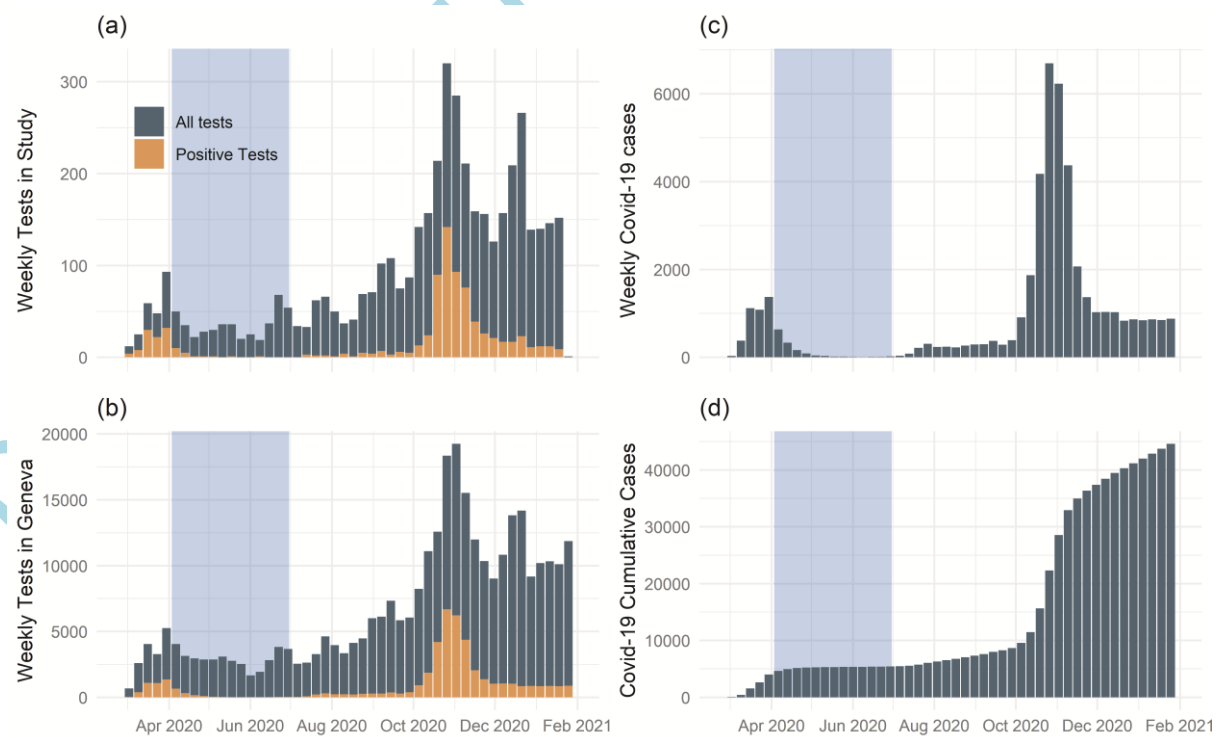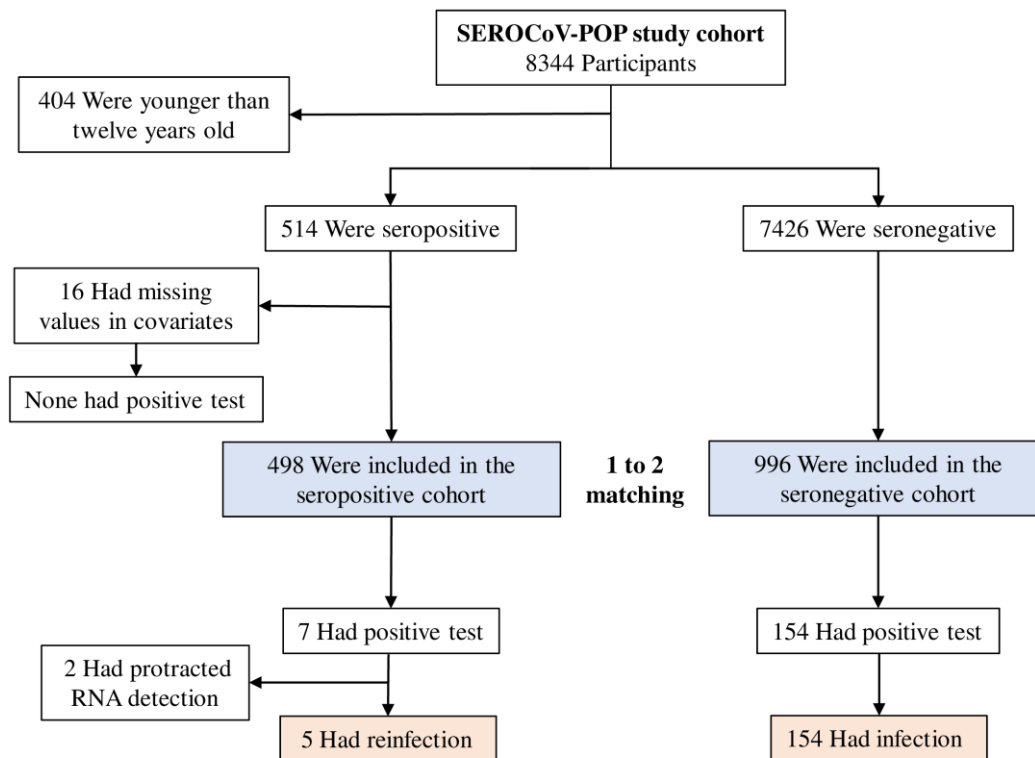**Figure 3. Infection-free survival according to serostatus**

Figure 1

Figure 2

Figure 3