Short Communication
SARS-CoV-2 seropositivity and subsequent infection risk: a prospective cohort study

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ABSTRACT

Objectives: This aim of this study was to examine the relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seropositivity and subsequent infection.

Design: A cohort study design was employed.

Methods: Stratified random sampling was undertaken to identify individuals aged 10 years and above registered with Qatar’s largest primary healthcare provider. A questionnaire was administered, and blood samples were collected and analyzed for immunoglobulin G antibodies against SARS-CoV-2 at baseline. Participants were followed up until March 31, 2021 (a 34-week follow-up period) for vaccination status and a positive polymerase chain reaction (PCR) test for SARS-CoV-2.

Results: A total of 2044 individuals participated in the study (97.2% of the planned sample). Of these, 185 (9%) were found to be seropositive at baseline. 450 individuals were vaccinated during the follow-up period — 246 with one dose and 204 with two doses. 86 (4.2%) individuals had a positive PCR test during the follow-up period, of which 80 (3.9%) were seronegative and six (0.3%) were seropositive (five undiluted and one with a titer ≥ 1:8). Overall, the findings suggest that reinfections are uncommon. Antibody concentrations potentially influence the risk of subsequent infection. Therefore, it might not be necessary to subject seropositive individuals to vaccination and the quarantine policies that apply to seronegative individuals.

As of September 28, 2021, over 18 months since the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported, 231 416 660 cases and 4 741 330 deaths had been reported globally (World Health Organization, 2021). Continued community transmission of SARS-CoV-2 has been observed in many countries. While reinfection is uncommon, it is a possibility. Currently, there is limited evidence on the role of antibodies (due to previous infection) with regard to subsequent infection. Several serological studies have reported on the risk of reinfection in seropositive individuals in various contexts (Kohler et al., 2021; Kurtikov et al., 2021; Hall et al., 2021; Leidi et al., 2021; Leidi et al., 2022). These included healthcare workers, residents of long-term care facilities, and essential workers. Follow-up durations for these study cohorts ranged from 5 weeks to 10 months. The findings indicated that SARS-CoV-2 antibodies provide between 80% and 94% protection against reinfection. Some studies have compared reinfections between symptomatic and asymptomatic initial infections and between different age groups. However, these studies did not report findings in relation to antibody titers prior to subsequent infection.

Our study examined the relationship between seropositivity and subsequent infection, specifically with regard to the role of antibody titer concentration in relation to the risk of subsequent infection. Individuals aged 10 years and above, registered with the Primary Health Care Corporation (PHCC), Qatar’s largest primary healthcare provider, were eligible for inclusion. Approximately 70% of Qatar’s population is registered with the PHCC across 27 primary healthcare centres. A stratified random sampling by age, gender, and nationality strata was used to identify a representative sample (N = 2012) of the total PHCC¬registered population (N = 1 063 243) (Figure 1).

Randomly identified individuals were invited to a PHCC health centre in July 2020. A questionnaire was administered, and blood samples were collected and analyzed for immunoglobulin G antibodies against SARS-CoV-2 at baseline. 150 μL of plasma was used for detection of anti-SARS-CoV-2 immunoglobulin G (IgG) using the CL-900i Chemiluminescence Immunoassay System (Mindray Bio-Medical Electronics Co, Shenzhen, China), according to the manufacturer’s instructions. Immunoglobulins were directed against the spike protein (S subunit).

Participants were followed up until March 31, 2021 (a 34-week follow-up period) for vaccination status and a positive polymerase chain
reaction (PCR) test for SARS-CoV-2. For the PCR tests, RNA was extracted and isolated prior to amplification on various platforms. Extracted nucleic acid underwent thermal cycling on ABI 7500 Thermal Cyclers (ThermoFischer, USA) using a range of thermal mixes. PCR tests were conducted if participants reported contact with a suspected or confirmed case, or if they had COVID-19 symptoms during the follow-up period. ‘Subsequent infection’ was defined as a positive PCR test in seropositive participants during the follow-up period.

Cox-regression was undertaken to assess the risk (hazard ratio [HR]) of a positive PCR test during the follow-up period. The analysis was adjusted for age, gender, comorbidities, and serology status. Survival analysis was also undertaken. The analyses took into account vaccination status and excluded individuals 2 weeks from the date of receiving the first dose.

A total of 2044 individuals participated in the study (97.2% of the planned sample). Of these, 185 (9%) were found to be seropositive at baseline. 450 individuals were vaccinated during the follow-up period — 246 with one dose and 204 with two doses. 86 (4.2%) individuals had a positive PCR test during the follow-up period. Of these, 80 (3.9%) were seronegative and six (0.3%) were seropositive (five undiluted and one with a titer ≥ 1:8).

Individuals aged 18–39 years (HR 2.22) and 40–59 years (HR 2.20) were at a higher risk of a positive PCR test compared with those aged 10–17 years (Table 1). Males were at a higher risk (HR 1.45) compared with females. Diagnoses of cerebrovascular disease (HR 7.11), arthritis (HR 2.04), dyslipidemia (HR 1.63), and diabetes mellitus (HR 1.21) were found to increase the risk of a positive PCR test. Seropositive individuals with an undiluted titer (HR 0.91) had a lower risk of subsequent infection compared with seronegative individuals. Those with a higher antibody titer (≥ 1:8) had an even lower risk (HR 0.31). The overall mean survival time to a positive PCR test was 33.22 weeks.

Only 3.2% of seropositive individuals had a subsequent infection during the follow-up period. This figure was higher than that reported by Vitale et al. for a cohort of seropositive individuals followed up for a period of 1 year, with a reported reinfection rate of 0.31% (Vitale et al., 2021).

Older adults (60+) had a lower risk of a subsequent infection compared with younger individuals. In contrast, Leidi et al. (2021) reported a higher risk in participants aged 60+. The majority of comorbidities (cerebrovascular disease, arthritis, dyslipidemia, diabetes) included in our study showed a higher risk of subsequent infection. However, Leidi et al. (2021) reported a lower risk in individuals with comorbid-

### Table 1
Risk of a positive PCR test by age, gender, comorbidity, and serology status

| Comorbidity                      | Adjusted hazard ratio | p-value |
|----------------------------------|-----------------------|---------|
| Arthritis                        | 2.04                  | 0.49 [NS]|
| Cardiovascular disease           | 0.35                  | 0.31 [NS]|
| Diabetes mellitus                | 1.21                  | 0.59 [NS]|
| Dyslipidemia                     | 1.63                  | 0.13 [NS]|
| Hypertension                     | 0.50                  | 0.09 [NS]|
| Cerebrovascular disease          | 7.11                  | 0.06 [NS]|
| Thyroid disorder                 | 0.64                  | 0.35 [NS]|
| Serology status                  |                       |         |
| Seropositive (undiluted) compared with seronegative | 0.91 | 0.84 [NS] |
| Seropositive (titre ≥ 1:8) compared with seronegative | 0.31 | 0.24 [NS] |

p (model) = 0.045
NS = not significant
ties. These different findings must be compared and interpreted with caution, due to differences in the study populations and the low numbers of subsequent infections.

While no differences in risk over time were observed between seropositive and seronegative individuals, antibody titer concentration appeared to play a role in defining the risk of subsequent infection. Those with a titer $\geq 1:8$ has a lower risk by one-third. A recent study reported that seropositive individuals had about one-fifth the risk of subsequent infection compared with seronegative individuals (Letizia et al., 2021). However, this only included healthy 18–20 year-olds, with a follow-up of 6 weeks.

The key strengths of our study were the random selection of participants from the PHCC-registered population and the long follow-up duration. A limitation of the study was the lack of statistically significant results due to the small number of subsequent infections in the cohort that was followed up. However, this limitation is unlikely to have impacted the results of the study.

Overall, the findings suggest that reinfections are uncommon. Antibody concentrations potentially influence the risk of subsequent infection. Therefore, it might not be necessary to subject seropositive individuals to vaccination and the quarantine policies that apply to seronegative individuals.

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**Ethical Approval**

This study was conducted with integrity according to generally accepted ethical principles and was approved by the Primary Health Care Corporation’s Research Sub-committee (ref. PHCCDCR202103016). Informed consent was waived due to the retrospective nature of the study.

**Declaration of Competing Interest**

All authors declare no conflicts of interest.

**References**

Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, Wellington E, Cole MJ, Saei A, Ogutu B, Munro K, Wallace S, Kirwan PD, Shroyer M, Vusirikala A, Rokadiya S, Kall M, Zambron M, Ramnay M, Brooks T, Brown CS, Chand MA, Hopkins SS. SIREN Study Group. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative healthcare workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet 2021;397(10283):1459–69.

Kohler P, Güsewell S, Seneghini M, Egger T, Leal O, Brucher A, et al. Impact of baseline SARS-CoV-2 antibody status on syndromic surveillance and the risk of subsequent COVID-19 — a prospective multicenter cohort study. BMC Med 2021;19:270.

Krutikov M, Palmer T, Tut G, Fuller C, Shroyer M, Williams H, et al. Incidence of SARS-CoV-2 infection according to baseline antibody status in staff and residents of 100 long-term care facilities (VIVALDI): a prospective cohort study. Lancet Healthy Longev 2021;2:e362–70.

Leidl A, Koegler F, Dumont R, Dubos R, Zahalla ME, Piumatti G, Coen M, Berner A, Darbelay Farhoudmand P, Vetter P, Vuilleumier N, Kaiser L, Courvoisier D, Azman AS, Guessous I, Stringhini SEROCov-POP Study Group. Risk of reinfection after seroconversion to SARS-CoV-2: a population-based propensity-score matched cohort study. Clin Infect Dis 2021;ciab495 May 27.

Leidl A, Berner A, Roxane D, Dubos R, Koegler F, Piumatti G, Vuilleumier N, Kaiser L, Balavoine JF, Trono D, Pittet D, Chappuis F, Kherad O, Courvoisier D, Azman AS, Zahalla ME, Guessous I, Stringhini S. Occupational risk of SARS-CoV-2 infection and reinfection during the second pandemic surge: a cohort study. Occupational and Environmental Medicine 2022;79:116–19.

Letizia AG, Ge Y, Vangeti S, et al. SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study. Lancet Respir Med 2021;9(7):712–20. doi:10.1016/S2213-2600(21)00158-2.

Vitale J, Memoli N, Clerici P, et al. Assessment of SARS-CoV-2 reinfection 1 year after primary infection in a population in Lombardy, Italy [published online ahead of print, May 28, 2021]. JAMA Intern Med 2021. doi:10.1001/jamainternmed.2021.2959.

World Health Organization (WHO). COVID-19 Weekly Epidemiological Update (August 10, 2021). Available from https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—28-september-2021 [Accessed October 4, 2021].