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RESEARCH ARTICLE

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Do quantitative levels of antispike-IgG antibodies aid in predicting protection from SARS-CoV-2 infection? Results from a longitudinal study in a police cohort

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Abstract

In a COVID-19 sero-surveillance cohort study with predominantly healthy and vaccinated individuals, the objectives were (i) to investigate longitudinally the factors associated with the quantitative dynamics of antispike (anti-S1) IgG antibody levels, (ii) to evaluate whether the levels were associated with protection from SARS-CoV-2 infection, and (iii) to assess whether the association was different in the pre-Omicron compared with the Omicron period. The QuantiVac Euroimmun ELISA test was used to quantify anti-S1 IgG levels. The entire study period (16 months), the 11-month pre-Omicron period and the cross-sectional analysis before the Omicron surge included 3219, 2310, and 895 reactive serum samples from 949, 919, and 895 individuals, respectively. Mixed-effect linear, mixed-effect time-to-event, and logistic regression models were used to achieve the objectives. Age and time since infection or vaccination were the only factors associated with a decline of anti-S1 IgG levels. Higher antibody levels were significantly associated with protection from SARS-CoV-2 infection (0.89, 95% confidence interval [CI] 0.82–0.97), and the association was higher during the time period when Omicron was predominantly circulating compared with the ones when Alpha and Delta variants were predominant (adjusted hazard ratio for interaction 0.66, 95% CI 0.53–0.84). In a prediction model, it was estimated that >8000 BAU/mL anti-S1 IgG was required to reduce the risk of infection with Omicron variants by approximately 20%–30% for 90 days. Though, such high levels were only found in 1.9% of the samples before the Omicron surge, and they were not durable for 3 months. Anti-S1 IgG antibody levels are statistically associated with protection from SARS-CoV-2 infection. However, the prediction impact of the antibody level findings on infection protection is limited.

KEYWORDS
antispike-IgG, COVID-19, quantitaive antispike-IgG, SARS-CoV-2, serology

1 | INTRODUCTION

SARS-CoV-2 antibody tests have established their value in the field of epidemiological and immunological research. A number of immunoassays from different manufacturers are currently available.[1] Most of them provide semiquantitative results and measure a broad range of immune responses (i.e., IgG, IgM, or IgA) to antigens belonging to the viral nucleocapsid or spike protein of SARS-CoV-2.[2,3] Accumulating data suggest that high levels of anti-SARS-CoV-2 IgG in plasma correlate with the presence of neutralizing antibodies, which may correlate with protection against infection.[4,5]

From February 2021 to April 2022, we performed a sero-epidemiological study for a specific population in our geographic region. The cohort consisted of 1024 employees of the cantonal police Bern in Switzerland (i.e., a predominantly healthy population). Every 3–4 months, a cross-sectional analysis was performed (five in total), in which we investigated the seroprevalence of semi-quantitative anti-SARS-CoV-2 antibodies (Elecsys® and Elecsys S®; Roche Diagnostics). The results of the five cross-sectional analyses are presented elsewhere.[6–8] Here, we present the results of the longitudinal analysis over the 16-month period. We reanalyzed the samples by using a novel quantitative antispike (anti-S1) IgG antibody immunoassay (QuantiVac®; Euroimmun).[9]

The study included three objectives. First, we investigated factors associated with the dynamics of the quantitative anti-S1 IgG antibody levels. Second, we evaluated whether the antibody levels were associated with protection from SARS-CoV-2 infection, irrespective of disease severity. In these two objectives, we differentiated between samples obtained before the onset of the first Omicron surge in Switzerland (i.e., first to fourth cross-sectional analysis from February to December 2021) and samples obtained over the entire study period (i.e., first to fifth cross-sectional analysis from February 2021 to April 2022). Third, we analyzed whether the quantitative levels of anti-S1 IgG antibody levels before the Omicron surge (i.e., at the fourth cross-sectional analysis in December 2021) predicted protection from infection with an Omicron variant in the upcoming 90–100 days.

2 | METHODS

A more detailed description of the methods is available in the Supporting Information.

2.1 | Study design and participants

The entire police cohort consisted of 4909 samples from 1024 study participants, collected from February 2021 to April 2022. Over this period, the proportion of individuals who were neither vaccinated nor infected decreased from 86.2% to 3% (Supporting Information: Figure S1).

The samples specifically selected for this study included all those with reactive anti-S1 IgG antibody levels. The three-step selection process from the entire cohort (4909 samples of 1024 study participants) to the final selected number of samples for this study (3219 samples from 949 study participants) is illustrated in Supporting Information: Figures S2–S4. In brief, samples with measurable levels in the previous semiquantitative antibody tests, in addition to samples from individuals with a history of a positive SAR-CoV-2 test result, and from vaccinated individuals were screened for the presence of reactive anti-S1 IgG antibodies.

2.2 | Longitudinal analysis with and without exposure to Omicron variants

Considering the different viral characteristics of Omicron variants and corresponding host response in comparison to previous SARS-CoV-2 variants, we categorized the analysis into two periods: one including samples from the entire study period (3219 samples from 949 study participants, as outlined in the previous paragraph), and one including all samples before the epidemiological onset of the Omicron surge (2310 samples from 919 study participants, Supporting Information: Figure S5). The Omicron sub-lineages BA.1 and BA.2 became predominant in Switzerland from late December 2021 (Supporting Information: Figure S1). Exposure to Omicron variants was defined on the basis of epidemiological data and not on sequencing of samples from individuals. It was defined as a reported positive SARS-CoV-2 test from a nasopharyngeal or saliva sample (antigen- or PCR-based tests) dated December 21, 2021, or later. On this date, the Swiss national surveillance data reported that more than 50% of the sequenced samples belonged to the Omicron variants.[10] On January 8, 2022, 90% of sequenced samples belonged to the Omicron variants.[10]

2.3 | Antispike IgG antibody levels before the Omicron surge

To investigate whether the quantitative anti-S1 IgG levels before the Omicron surge predicted protection from infection, we included only samples available at the fourth cross-sectional analysis collected from December 1st to 22nd, 2021, and only from individuals with responses to questions on infection and vaccine dates; 895 samples from 895 individuals were included for this analysis (Supporting Information: Figure S6).

2.4 | Antibody assays

The Anti-SARS-CoV-2-QuantiVac-ELISA IgG (Euroimmun), which uses a recombinant S1 domain (including the receptor binding domain, RBD) of the viral spike protein to specifically quantitate IgG class antibodies (referred to as anti-S1 IgG), was processed on an EUROIMMUN Analyzer I platform according to the manufacturer's instructions. A six-point calibration curve was applied to determine the exact IgG levels expressed as standardized binding antibody units (BAU)/mL. To quantitate high-level samples, we used four dilution assays covering different antibody ranges (3.2–384 BAU/mL, 320–3840 BAU/mL, 960–11 520 BAU/mL, 3200–38 400 BAU/mL). The samples were retested until the results fell into a valid range. The antibody concentrations were interpreted as follows: <25.6 BAU/mL negative, ≥25.6–<35.2 BAU/mL borderline, and ≥35.2 BAU/mL positive, whereby borderline data were considered positive for statistical analyses. According to the manufacturer, the specificity of the test is 99.8%.

2.5 | Statistical analysis

To describe the characteristics of the study cohort, we used mean ± standard deviation (SD) or median with interquartile range (IQR) for summarizing continuous variables, as appropriate.

The analysis of the quantitative antibody levels over time was performed with a mixed-effect linear model. To analyze the association between anti-S1 IgG levels and protection from infection, we used a mixed-effect time-to-event model, a mixed-effect Cox regression and logistic regression models. A detailed description of the statistical methods is provided in the Supporting Information. All analyses were performed with R (version 4.2.1).

2.6 | Clinical trial registration

The study was registered at ClinicalTrials.gov NCT04643444.

3 | RESULTS

3.1 | Characteristics and antispike antibody levels

The characteristics of the 949 included study participants are illustrated in Table 1. They mirror the relatively low proportion of individuals with comorbidities in the entire police cohort (i.e., 22%).[6–8] The proportion dynamics of study participants with the first, second, and third vaccine dose and reported SARS-CoV-2 infections are illustrated in Figure 1. Between the fourth and fifth cross-sectional analysis, the numbers and infections during the Omicron surge increased considerably. In the same period, the third vaccine dose (i.e., booster) was administered to almost 70% of the included study participants. These two factors contributed to the observation that the highest median level of anti-S1 IgG was measured at the fifth cross-sectional analysis. On an individual level, the absolute antibody level values varied considerably (Supporting Information: Figure S7). High anti-S1 IgG level values were observed at the second cross-sectional analysis, reflecting the high proportion of vaccinated individuals shortly before serum sampling. However, these values rapidly declined within 3–4 months (i.e., at the third cross-sectional analysis).

3.2 | Factors associated with the dynamics of anti-S1 IgG

Age and days since infection or vaccination, but none of the comorbidities of the included study participants, were associated with a decrease in antibody levels (Supporting Information: Table S1). This finding was not observed for the first 11-month study period (i.e., first to fourth cross-sectional analysis) and before the Omicron surge.

3.3 | Anti-S1 IgG antibody levels are associated with protection from infection

Considering that the research question focused on prevention of the upcoming infection, reported infection dates from the first until the fifth cross-sectional analysis ($n = 343$ reported infection dates) and antibody level values of the first cross-sectional analysis until those of the fourth cross-sectional analysis were included for this analysis ($n = 2310$ samples). This approach allowed us to assess the infection risk in the time intervals

TABLE 1 Characteristics of included study participants.

Characteristics	No. of responses	Included study participants ($n = 949$)
Age (years), mean (SD)	859	41 (8.8)
Sex	945	
Female		256 (27%)
Male		689 (73%)
Comorbidity		
BMI (kg/m^2), mean (SD)	947	26 (3.5)
Diabetes mellitus	944	13 (1.4%)
Arterial hypertension	945	76 (8.0%)
Cardiovascular disease	942	17 (1.8%)
Lung disease	944	25 (2.6%)
Immunosuppression	943	12 (1.3%)
Other disease	945	95 (10%)
No comorbidity	949	737 (78%)

Abbreviations: BMI, body mass index; SD, standard deviation.

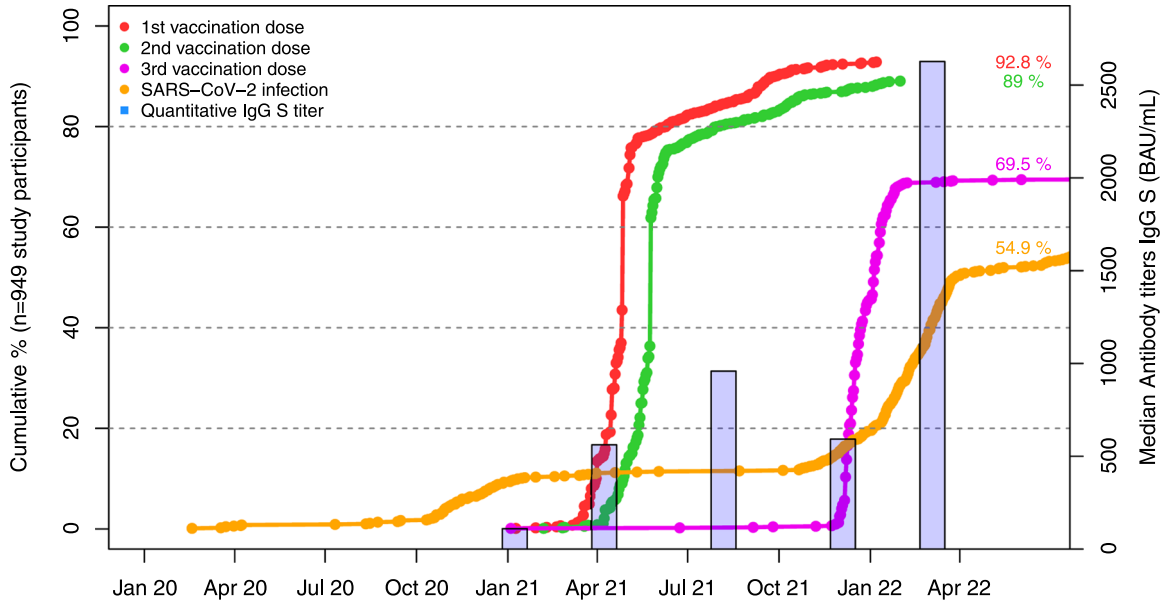

FIGURE 1 Vaccine and reported rates and median quantitative antispike IgG values of the included study participants within the police cohort. All included study participants had either experienced a SARS-CoV-2 infection (symptomatic or asymptomatic) or were vaccinated with a COVID-19 vaccine or both, since they all had reactive antibodies (see Supporting Information: Figures S2–S4). The blue bars (quantitative antispike IgG antibody levels) are inserted at each cross-sectional analysis. The median values at the first, second, third, fourth, and fifth cross-sectional analysis were 109.7, 561.6, 958.7, 592.3, and 2627.02 BAU/mL, respectively (see also Supporting Information: Figure S7). The red, green, and purple curves illustrate the cumulative vaccine rates over time. The orange curve illustrates the cumulative self-reported infection dates collected from questionnaires.

TABLE 2 Association with anti-S1 IgG antibody levels and infection risk reduction.

A. Time-to-event analysis to measure the effect of quantitative anti-S1 IgG antibody levels as protection from SARS-COV-2 infection over the entire study period		
Independent variables, *n* = 2310		**HR (95% CI)**
Logarithmic anti-S1 IgG antibody levels		0.89 (0.82–0.97)
B. Adjusted time-to-event analysis to measure the effect of quantitative anti-S1 IgG antibody levels as protection from SARS-COV-2 infection		
Independent variables, *n* = 2310 **Adjusted variables**	**Adjusted HR (95% CI)** **Index period**	**Adjusted HR (95% CI)** **Index periodanti-S1 IgG levels**
Logarithmic anti-S1 IgG antibody levels	0.85 (0.77–0.93)	1.16 (0.94–1.42)
Index period	10.7 (8.05–14.32)	158 (33–759)
Interaction	–	0.66 (0.53–0.84)

Note: Index period calculations included the comparison of the periods before and after the onset of the Omicron surge.
Abbreviations: anti-S1, antispike; CI, confidence interval; HR, hazard ratio.

between the cross-sections as well as together over the entire study period. The results are illustrated in Table 2.

First, a time-to-event (i.e., infection) analysis without adjustments over the entire study period was performed. It revealed a hazard ratio (HR) of 0.89 (95% confidence interval [CI] 0.82–0.97), indicating an association between anti-S1 IgG levels and prevention of infection (i.e., risk reduction for infection, Table 2).

Second, after adjustment for two time periods (i.e., before and after the defined time point for the onset of the Omicron surge), the HR was similar (0.85, 95% CI 0.77–0.93). The risk for infection was considerably higher when the Omicron period was compared with the previous episodes of the pandemic (adjusted HR 10.7, 95% CI 8.05–14.32, Table 2).

Third, the model was adjusted for the time periods and the levels of anti-S1 IgG levels. Then, the association with anti-S1 IgG was not significant and the risk of Omicron infection increased by more than 10-fold (adjusted HR 158, 95% CI 33–759). However, the interaction between the two variables "anti-S1 IgG levels" and "the time period" was significant (adjusted HR 0.66, 95% CI 0.53–0.84; Table 2), indicating that the association of anti-S1 IgG levels and protection from infection was higher during the Omicron period, though much higher antibody levels are required for protection.

Fourth, anti-S1 IgG levels were categorized in three equally distributed groups (i.e., tertials) among the included samples for this analysis ($n = 2310$) based on their quantitative values (25–400, 401–1188, and >1188 BAU/mL). The cumulative incidences of infection for each of these tertials were determined over the upcoming 3 months in association with days since the serum sampling. The results were then implemented in a prediction model and separated into the two time periods (i.e., before and after the defined time point for the onset of the Omicron surge, Figure 2). These results indicate that the quantitative levels of anti-S1 IgG levels are associated with prevention of SARS-CoV-2 infection, and confirmed the aforementioned results that prevention from Omicron variants requires much higher antibody levels in comparison to other SARS-CoV-2 variants. In the prediction model, it was estimated that more than 8000 BAU/mL anti-S1 IgG was required to reduce the risk of infection with an Omicron variant by approximately 20%–30% for 90 days. The proportion of samples with a value above 8000 BAU/mL anti-S1 IgG was 3.5% for the entire cohort and, 0%, 6.2%, 0.2%, 1.6%, and 7.5%, for each cross-section analysis (i.e., first to fifth), respectively (Supporting Information: Figure S7). When considering all samples before the onset of the Omicron variants, values above 8000 BAU/mL were only found in 1.9%. Notably, such high levels were not durable over two sampling periods (i.e., 3–4 months).

These results taken together, indicate that, before the Omicron surge, the association of quantitative anti-S1 IgG levels and prevention of infection was less significant than it was during the Omicron surge. In the pre-Omicron period, the infection rate was low, the vaccination rate high (Figure 1) and the quantitative increase in anti-S1 IgG levels had little effect in preventing more infections. Conversely, in the prediction model, the quantitative increase in anti-S1 IgG levels had more effect in preventing infection with an Omicron variant, though high antibody levels were required to achieve this effect (Figure 2). Such high levels were only rarely detected in our cohort, and if so, they were not durable.

3.4 | Protection from infection due to Omicron variants is higher when anti-S1 IgG antibody levels are derived from infection plus vaccination in comparison with antibody levels from vaccination only

Considering the high transmissibility of the Omicron variants, we specifically focused on anti-S1 IgG antibody levels before the Omicron surge (i.e., samples obtained at the fourth cross-sectional analysis). The study population included 895 samples and study participants (Supporting Information: Figure S6). Although all of them had reactive anti-S1 IgG, only 33 (3.7%) were never vaccinated. Their antibody levels derived from (symptomatic or asymptomatic) infection. In the other 862 (96.3%) study participants, antibody levels derived from vaccines with or without a previous non-Omicron variant infection; 124 (13.9%) reported a positive SARS-CoV-2 test result. The proportion of infected individuals ($n = 33$ nonvaccinated

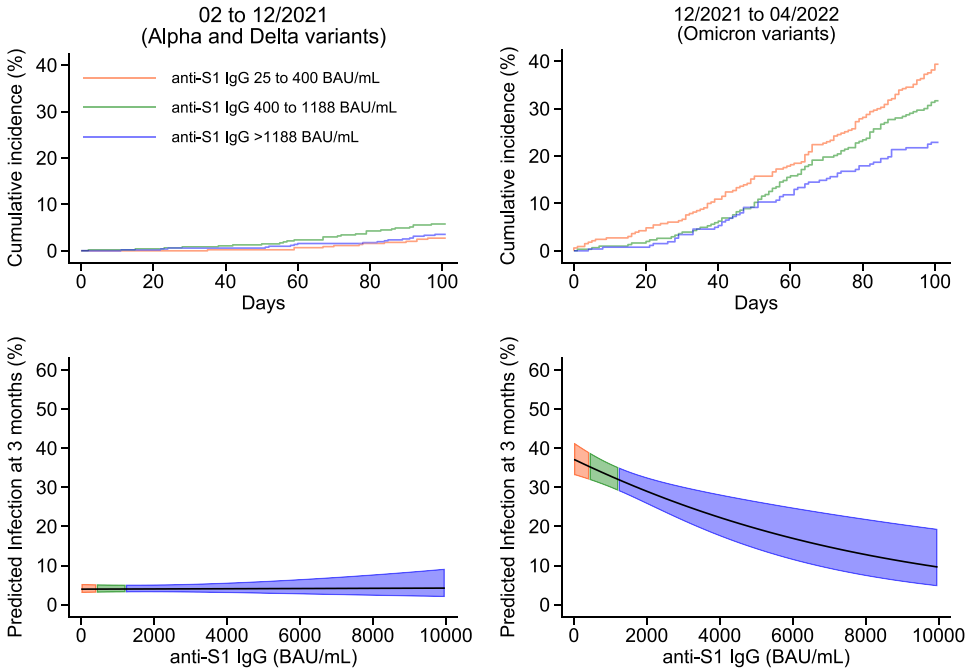

FIGURE 2 Cumulative incidence and predicted risk for SARS-COV-2 infection according to quantitative antispike (anti-S1) IgG antibody levels and time periods during the pandemic. Among the included samples for this analysis ($n = 2310$), anti-S1 IgG levels were categorized in three equally distributed groups (tertials) based on their quantitative values. Kaplan–Meier graphs: The upper graphs illustrate the reported cumulative incidence of SARS-CoV-2 over 3 months in association with days since serum sampling in which the corresponding quantitative anti-S1 IgG levels were determined. The lower graphs illustrate the results from the prediction model. The colors correspond to the categorized anti-S1 IgG levels (red 25–400 BAU/mL, green 400–1188 BAU/mL, blue >1188 BAU/mL).

+124 vaccinated plus infected = 157 of 895, 17.5%) is similar to that of our previous investigation with different methods (i.e.; 19% in Sendi et al.[7]). Thus, out of these 895 samples, the majority of this group were individuals who were vaccinated without a previous SARS-CoV-2 infection.

Among the 895 study participants, 249 (27.8%) had already received the third dose of the COVID-19 vaccine within a median of 7 (IQR 4–13) days before serum sampling. In these samples, measured quantitative anti-S1 IgG levels before the Omicron surge were likely influenced by the vaccine dose. The proportion of individuals with a third vaccine dose then gradually increased after the serum sampling, while infection cases due to Omicron variants were rising in parallel (Figure 1 and Supporting Information: Figure S1).

Of the 895 study participants, 337 (37.7%) reported a SARS-CoV-2 infection during the Omicron surge, while 558 (62.3%) reported no infection. Among the 337 participants who reported a SARS-CoV-2 infection during the Omicron surge, 242 (71.8%) received the vaccine booster dose before the infection. Only in 5 (2.1%) of them was the time interval between the dates of vaccine administration and a positive infection test result <7 days, and in 230 (85.1%) individuals, the time interval was ≥14 days. From these data and our previous investigation,[7] it appeared that the booster dose did not prevent infection with an Omicron variant. Therefore, we investigated with two different statistical approaches whether there was still an association with anti-S1 IgG levels and protection from infection. For these analysis, we considered only samples that were obtained shortly before the Omicron surge (Table 3).

First, we performed a logistic regression model and adjusted it for infection and vaccination. The levels of anti-S1 IgG antibody levels were associated with protection from infection. The adjusted odds ratio (OR) was lowest when a previous infection was reported (0.39, 95% CI 0.24–0.61). This association of infection risk reduction was weaker in individuals with vaccination only and not statistically significant (Table 3).

Second, a time-to-event analysis (i.e., infection up to 90 days) was performed. Again, the anti-S1 IgG antibody levels were associated with protection from infection. The adjusted OR was lowest when a previous infection was present (0.47, 95% CI 0.31–0.69). Similar to the first analysis, this association was weaker and not significant in individuals with vaccination only (Table 3).

Finally, we performed a sensitivity analysis, because the major peak of the Omicron surge was in-between two blood sampling periods (Supporting Information: Figure S1A) and because it is possible that study participants with a booster had higher anti-S1 IgG antibody levels in the study interval between the fourth and fifth cross-section analysis. In the sensitivity analysis, samples from study participants with a booster vaccination after measurement of antibody levels were excluded. The results of this subset (n = 489) were very similar to those with the entire sample selection (Supporting Information: Table S2A,B).

Because of the low proportions of study participants who were not vaccinated (3.7%), further categorization into more differentiated groups did not reveal more statistically significant results (Supporting Information: Table S3). However, the association of risk reduction remained statistically significant for the anti-S1 IgG antibody levels (adjusted OR 0.87, 95% CI 0.77–0.99), and there was a strong trend of risk reduction for individuals with previous infection plus vaccination (adjusted OR, 0.31, 95% CI 0.09–1.04).

4 | DISCUSSION

The aim of this study was to better understand the relationship between quantitative anti-SARS-CoV-2 IgG antibody levels and protective antiviral immunity following infection or vaccination. The

TABLE 3 Association with anti-S1 IgG antibody levels and infection risk reduction with an Omicron variant based on previous infection and vaccination status.

A. Logistic regression to measure the effect of anti-S1 IgG antibody levels, previous infection and vaccination as protection from an infection with the Omicron variant		
Independent variables, n = 895	**OR (95% CI)**	**Adjusted OR (95% CI)**
Logarithmic anti-S1 IgG antibody levels	0.80 (0.71–0.90)	0.85 (0.75–0.96)
Previous infection with non-Omicron variants	0.38 (0.24–0.58)	0.39 (0.24–0.61)
Vaccination	0.81 (0.40–1.67)	0.64 (0.29–1.41)
B. Time-to-event analysis (i.e., infection up 90 days) to measure the effect of anti-S1 IgG antibody levels, infection and vaccination as protection from an infection with the Omicron variant		
Independent variables, n = 895	**HR (95% CI)**	**Adjusted HR (95% CI)**
Logarithmic anti-S1 IgG antibody levels	0.83 (0.76–0.91)	0.87 (0.79–0.96)
Previous infection with non-Omicron variants	0.45 (0.31–0.66)	0.47 (0.31–0.69)
Vaccination	0.79 (0.46–1.35)	0.67 (0.38–1.19)

Note: The middle column represents the results from unadjusted calculations and the right column from adjusted calculations.
Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

investigation was performed in a cohort with predominantly healthy and vaccinated individuals. After a meticulous selection process, 3219 samples of 949 participants with available vaccination and infection dates were included. We observed, consistent with the findings of others,[11,12] an association between a decline in antibody levels and increasing age and days since infection or vaccination. In all analyses, we observed a statistically significant association between higher anti-S1 IgG levels and infection risk reduction. The statistical association was higher during the Omicron surge, indicating that the differences in antibody anti-S1 IgG levels were less relevant in the pre-Omicron period than during the Omicron period, and that the vaccine provided a protective immune response against Alpha and Delta variants.[13] The statistical models indicated that the higher the antibody anti-S1 IgG levels during the Omicron period, the higher the risk reduction of infection, although, in the prediction model, very high anti-S1 IgG levels were estimated to reduce the risk of infection with Omicron variants by only approximately 20%–30% for a short period (Figure 2). In none of the serum sampling time points did the median cohort values of anti-S1 IgG antibody levels achieve such high levels, and no individual demonstrated such high levels for 3 months (i.e., at two consecutive sampling periods, Supporting Information: Figure S7). However, individuals who had a previous infection and vaccination (so-called hybrid immunity) had a lower risk of infection with Omicron variants.

Most serological studies postulate the level of protection from infection on the basis of neutralization test results in the laboratory[14] and, accordingly, call new SARS-CoV-2 variants "escape mutants."[15] Neutralization tests are time-consuming and their results may be heterogenous and difficult to interpret.[16,17] In the literature, two consecutive correlation hypotheses are often used, namely, that SARS-CoV-2 anti-S1 IgG antibody levels correlate with neutralization activity,[5,9,18,19] and that neutralization activity may correlate with protection from infection.[20] This study investigated the direct relationship between quantitative anti-S1 and positive test results in individuals followed longitudinally over 16 months. Thus, quantitative anti-S1 IgG antibody levels may be a surrogate marker for neutralizing antibodies. We used a rigid screening procedure before analyzing the samples for the presence of quantitative anti-S1 IgG because the sensitivity may be lower when these tests are used as a screening method.[19] All serum samples were tested with the same assays for this study because agreement between quantitative ELISAs is variable and cannot be used interchangeably despite calibration against a standard.[21] Therefore, we are convinced that our serological results are robust.

The results contribute to our understanding of the protective role of anti-S1 IgG against SARS-CoV-2. In this cohort, a high vaccination rate and a low infection rate were observed during the first 11 months of the study period.[7,8] COVID-19 vaccines do generate anti-S1 IgG,[22–24] and a significant association between the anti-S1 IgG levels and infection risk reduction was observed in this study. In the prediction model, values above 900 BAU/mL added little to the infection risk reduction in the pre-Omicron period.

Consistent with laboratory studies demonstrating that much higher antibody levels are required to neutralize Omicron variants in comparison to previous SARS-CoV-2 variants,[15] measured anti-S1 IgG levels in our cohort were insufficient to prevent an infection with an Omicron variant in a considerable proportion of the study participants. The significant statistical interaction between the Omicron period and antibody levels indicated that higher antibody levels are required to prevent infection. The prediction model, together with our measured values, however, estimated that these high anti-S1 IgG levels are rarely achieved either by vaccination or by infection, and if so, they decline within 3 months. This finding is consistent with that of other investigators, demonstrating the limited and short duration of vaccine efficacy of boosters against mild infection with Omicron variants.[25] Hence, in healthy vaccinated individuals (with or without infection), it is not meaningful to measure quantitative anti-S1 IgG to estimate an upcoming infection risk with an Omicron variant reliably.

Our study has limitations. Alongside our study aim, only those with reactive anti-S1 IgG antibody levels were analyzed. Therefore, this study does not answer the question whether the presence of anti-S1 antibodies (irrespective of their levels) per se is a measure of protection. Mitigation measures to prevent transmission (including survey data on mitigation practices, e.g., wearing masks) have been reported in the previously published cross-section results of this cohort.[6–8] They changed over the study period of 16 months, and we are unable to control for this variable over the entire study period in this longitudinal analysis. Because mitigation practices likely influence the transmission rate, it is possible that the association between anti-S1 antibody levels and protection might be different if these could have been controlled for.

In the final questionnaire at the end of the study period, we asked participants for the date of positive results from a SARS-CoV-2 test, and not the date of the onset of symptoms, because this approach minimized recall bias. Because the definition of infection in this study was based on self-reported test results, non-tested asymptomatic infections were missed and we may have underestimated the true numbers of infected individuals. However, in our previous five cross-sectional analyses, a different infection definition was used. It included individual questionnaires on symptoms and antinucleocapsid antibody seroconversion within 3 months,[6–8] and the results were in the same range as those in the present study (range +/−1.5%). All infection dates were reviewed for accuracy, and we excluded samples with missing dates. In our view, the possibly missed proportion of non-tested asymptomatic infections is unlikely to change the overall results of this study. For the variable SARS-COV-2 infection, we did not differentiate between disease severity, as this was investigated in our previous cross-sectional studies.[6–8] Our statistical prediction models are theoretical and may be imprecise. Nonetheless, the results fit well with our observations and that of others.[25] Finally, the cohort consists of predominantly healthy and vaccinated individuals and the results of this analysis may not be uncritically extrapolated to other settings.

In conclusion, we found a statistically significant relationship between the quantitative anti-S1 IgG antibody levels and infection risk reduction in a 16-month longitudinal study. The association between the pre-Omicron period and during the Omicron surge was distinct. The higher statistical association of anti-S1 IgG antibody levels in the Omicron period in comparison to the pre-Omicron period and the higher odds of being infected with an Omicron variant indicated that higher anti-S1 IgG levels are required to protect from an Omicron infection, although such high levels were rarely observed in our cohort, and if so, not for a prolonged time. These results indicate limited value of determining anti-S1 IgG levels for infection prediction in healthy vaccinated or infected individuals.

ETHICS STATEMENT

All participants gave written informed consent to participate in the PoliCOV-19 study. The study protocol complied with the Declaration of Helsinki and applicable local legal provisions and was approved by the Cantonal Research Ethics Commission of Bern, Switzerland (ID-2020-02650).

AUTHOR CONTRIBUTIONS

Parham Sendi, Marc Thierstein, Rossella Baldan, and Christoph Niederhauser designed the study, were responsible for the conduction of the study, and Parham Sendi wrote the first draft of the manuscripts. Nadja Widmer, Peter Gowland, Caroline Tinguely, and Christoph Niederhauser were responsible for performing the assays and data transfer. Annina Elisabeth Büchi was responsible for data monitoring. Mattia Branca and Dik Heg performed the statistical analysis. Dominik Güntensperger was responsible for data management. Manuel Raphael Blum, Elitza S. Theel, Elie Berbari, and Andrea Endimiani contributed to the study design and research analysis and provided their scientific expertise for this study. All authors revised the first draft, read, and approved the final manuscript. Open access funding provided by Universitat Bern.

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CONFLICT OF INTEREST STATEMENT

Elitza S. Theel is advisory board/Consultant for Roche Diagnostics, Euroimmun US, and Serimmun Inc., but was never involved in the decision-making for acquiring antibodies for the purpose of this study. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data presented in the manuscript is not publicly available. Coded data may be requested from the corresponding author for nonprofit and justified scientific reasons from academic institutions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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