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Original Article

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Development of hybrid immunity during a period of high incidence of Omicron infections

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Abstract

Background: Seroprevalence and the proportion of people with neutralizing activity (functional immunity) against SARS-CoV-2 variants were high in early 2022. In this prospective, population- based, multi-region cohort study, we assessed the development of functional and hybrid immunity (induced by vaccination and infection) in the general population during this period of high incidence of infections with Omicron variants.

Methods: We randomly selected and assessed individuals aged ≥16 years from the general population in southern ($n = 739$) and north-eastern ($n = 964$) Switzerland in March 2022. We assessed them again in June/July 2022, supplemented with a random sample from western ($n = 850$) Switzerland. We measured SARS-CoV-2 specific IgG antibodies and SARS-CoV-2 neutralizing antibodies against three variants (ancestral strain, Delta, Omicron).

Results: Seroprevalence remained stable from March 2022 (97.6%, $n = 1894$) to June/July 2022 (98.4%, $n = 2553$). In June/July, the percentage of individuals with neutralizing capacity against ancestral strain was 94.2%, against Delta 90.8% and against Omicron 84.9%, and 50.6% developed hybrid immunity. Individuals with hybrid immunity had highest median levels of anti-spike IgG antibodies titres [4518 World Health Organization units per millilitre (WHO U/mL)] compared with those with only vaccine- (4304 WHO U/mL) or infection- (269 WHO U/mL) induced immunity, and highest neutralization capacity against ancestral strain (hybrid: 99.8%, vaccinated: 98%, infected: 47.5%), Delta (hybrid: 99%, vaccinated: 92.2%, infected: 38.7%) and Omicron (hybrid: 96.4%, vaccinated: 79.5%, infected: 47.5%).

Conclusions: This first study on functional and hybrid immunity in the Swiss general population after Omicron waves showed that SARS-CoV-2 has become endemic. The high levels of antibodies and neutralization support the emerging recommendations of some countries where booster vaccinations are still strongly recommended for vulnerable persons but less so for the general population.

Keywords: SARS-CoV-2, COVID-19, hybrid immunity, functional immunity, seroprevalence, neutralization, vaccination, infection, cohort, population-based

Key Messages

- Our study is one of the first that assessed infection-induced, vaccine-induced and hybrid immunity and neutralizing activity of antibodies against SARS-CoV-2 in a larger population-based sample.
- The population-based cohort study showed that by mid-2022, SARS-CoV-2 has become endemic and the levels of antibodies and neutralization against the ancestral strain, Delta, and Omicron variants were very high in the general Swiss population.
- Hybrid immunity confers higher levels of neutralizing activity compared with both vaccine-induced and infection-induced immunity.
- The high levels of antibodies and neutralization support the emerging recommendations of some countries where booster vaccinations are still strongly recommended for vulnerable persons but less strongly recommended for the general population.

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Introduction

The World Health Organization (WHO) emphasized in June 2022 the key importance of continuous monitoring of immunity against SARS-CoV-2 and its variants of concern (VOC) in the general population, to inform public health measures and vaccination strategies.[1] Early seroprevalence studies in spring 2020 showed that up to 10% of the general population had already developed antibodies against SARS-CoV-2 after the first wave in Europe and North America.[2–5] Up to the point where vaccinations were approved in late 2020, seroprevalence increased to, on average, 25% as a consequence of SARS-CoV-2 infections, but with great variations within and across countries.[1,6,7] Following the introduction of vaccines, seroprevalence quickly increased to around 50% in the general population worldwide and to above 90% in high-income countries.[6,8] The lower rate of severe COVID-19 in vaccinated individuals provides strong support for the effectiveness of vaccines. However, although vaccines confer very high individual protection against COVID-19 symptoms, hospitalization and deaths, protection against new infections is partial and may decrease over time and with the emergence of new VOCs that can escape previously induced immunity.[9–11]

The rise of the highly infectious Omicron VOCs in early 2022 caused many infections in fully vaccinated or boosted persons. This led to a high seroprevalence and functional immunity in the general Swiss population, as measured by neutralizing activity of antibodies in serum.[12] Functional immunity contributes to protection from severe courses of COVID-19 and is stronger if induced by both vaccinations and infections than by either alone (i.e. hybrid immunity).[13–15] To inform public health measures and further booster vaccine strategies, it is important to assess population levels of seroprevalence and durability of functional and hybrid immunity developed during a time of high incidence of Omicron infections. The aim of this study was to assess the trajectory of anti-SARS-CoV-2 antibody titres and functional and hybrid immunity in the general population, and to compare such trajectories across age groups and three cantons, i.e. federal states of the Swiss confederation, covering the three main regions in Switzerland.

Methods

Study design, sampling, and participants

This prospective, population-based, multi-region cohort study is part of the Corona Immunitas research programme in Switzerland,[16,17] for which we had completed four Phases of seroprevalence studies between April 2020 and October 2021 using a standardized protocol (study registration: ISRCTN registry 18181860). The current study includes results from Phases 5 and 6, for which assessments were conducted between 1 March and 1 April 2022, and 30 May and 11 July 2022, respectively (detailed results of Phase 5 published elsewhere).[12]

In Phase 5, we randomly selected individuals from the general population in southern (canton of Ticino) and northeastern (canton of Zurich) Switzerland, who were assessed again in Phase 6. For cross-sectional analyses in Phase 6, we supplemented the southern and eastern Switzerland sample with a random sample from the general population in western Switzerland (canton of Vaud). Due to another seroprevalence study requested by the cantonal health authorities of Vaud, which took place in the autumn of 2021, the canton of Vaud only participated in Phase 6; it was not feasible to conduct an additional assessment between autumn 2021 and June 2022. The three Swiss cantons differ across demographic, sociocultural and linguistic aspects and climate, all of which may impact on the dynamics of the pandemic.[18] However, they are fairly representative for their language region (Italian, German, and French; map of Switzerland for overview see Supplementary Figure S1, available as Supplementary data at *IJE* online). The Swiss Federal Office of Statistics provided random samples of the general population in age-stratified (16–29, 30–44, 45–64 and ≥65 years) groups, separately for the cantons of Ticino, Vaud and Zurich. We selected these groups after consultation with the Swiss Federal Office of Public Health to adequately account for the potential impact on seroprevalence of social behaviour, adherence to public health measures and vaccination uptake, all of which differ across these age groups.[19] The target sample size was 200 for each age stratum in the three cantons (i.e. total planned sample size of 2400). Based on the framework proposed by Larremore *et al.*,[20] we deemed 200 participants to provide precise estimates; given a sensitivity of 97% and a specificity of 99% for the serological test we have used,[21] a population of 200 persons with 180 positive tests and 20 negative tests (observed prevalence 90.0%) yields a posterior prevalence of 92.3% with 90% credible intervals of 88.5 and 95.8 (Supplementary Figure S2, available as Supplementary data at *IJE* online). All Phase 5 participants in Ticino and Zurich were invited to participate in the Phase 6 blood sampling.

Data collection

We invited participants to in-person study visits at a health care facility to provide a blood sample. People who were not able or willing to travel were offered home visits. For each participant, trained personnel collected venous blood samples, according to clinical standards and COVID-19 hygiene measures. Before the first study visit, all participants completed a baseline questionnaire including information regarding sociodemographics, vaccinations, SARS-CoV-2 infections, hospital and intensive care unit (ICU) admissions, symptoms in case of infections and past medical history, using the secure, web-based Research Electronic Data Capture platform (REDCap) for data collection and management.[22,23] They also had the possibility to fill in the questionnaire in a paper/pencil version. Participants from the cantons of Ticino and Zurich who were recruited in Phase 5 were invited for a second study visit and blood sampling in Phase 6, 3 to 4 months later. Before this second study visit, participants filled in another questionnaire targeting the time between the first and second blood sampling including questions on new self-reported SARS-CoV-2 infections, symptoms and vaccinations.

Laboratory assays for SARS-CoV-2 antibodies and neutralizing capacity against SARS-CoV-2 variants

We assessed SARS-CoV-2 specific antibodies against the spike and nucleocapsid proteins using Sensitive Anti-SARS-CoV-2 Spike Trimer Immunoglobulin Serological (SenASTrIS), a Luminex binding assay.[21] The assay measures binding of IgG antibodies to the trimeric SARS-CoV-2 spike and the nucleocapsid proteins. The test has a high specificity (99%) and sensitivity (97%), has been validated in samples of the general population and in specific subgroups[21] and results in semi-quantitative median fluorescence intensity (MFI) values. The MFI values have additionally been translated to the WHO

units per millilitre (U/mL) scale as measured by the Elecsys Anti-SARS-CoV-2 immunoassay by Roche.[12] We also assessed the presence of SARS-CoV-2 neutralizing antibodies against three variants (ancestral strain, Delta and Omicron) that were dominant in Switzerland in 2022, using a cell- and virus-free assay.[24] This assay measures the proportion of antibodies that block the interaction of the angiotensin-converting enzyme 2 receptor (ACE2r) with the receptor-binding domain of the trimer spike protein of the ancestral strain and variants of concern. All analyses were performed in the laboratory of Immunology of the Lausanne University Hospital (CHUV).

Outcome definition

We defined seropositivity based on the presence of anti-spike IgG antibodies according to the threshold of SenASTrIS test positivity with MFI $\geq$6 (levels categorized: $\geq$6 and <12 low, $\geq$12 and <40 middle, $\geq$40 high) and neutralization capacity based on the cut-off value of the cell- and virus-free assay of 50. Functional immunity was defined based on neutralization capacity of the cell- and virus-free assay above the threshold value of 50. This was determined independently for each variant spike (ancestral strain, Delta, Omicron). Last, source of immune status was defined based on SARS-CoV-2 vaccination status (self-reported) and SARS-CoV-2 infection, determined as seropositivity for anti-nucleocapsid IgG (MFI$\geq$6), report of a positive polymerase chain reaction (PCR) or rapid antigen test or presence of anti-spike IgG antibodies in the absence of a SARS-CoV-2 vaccination. We categorized immune status as follows: immune naïve (i.e. no detectable antibodies and no reported infection or SARS-CoV-2 vaccination), vaccine-induced only, infection-induced only or hybrid immunity (SARS-CoV-2 vaccination and infection).

Statistical analysis

We used medians and interquartile ranges (numerical variables) or absolute numbers and percentages (categorical variables) for the descriptive analyses.

We calculated seroprevalence using a Bayesian logistic regression model adjusted for age group (16–29, 30–44, 45–64 and 65+) and sex with weak normal(0, 1) priors on beta coefficients per canton. We incorporated the uncertainty of sensitivity (hierarchical prior) and specificity [uniform(0, 1) prior] of the serological test as binomial models. We used a Markov chain Monte Carlo sampling approach with four chains (250 warm-up iterations and 1250 estimation iterations per chain, 5000 iterations in total with warm-up iterations not considered) using the probabilistic programming language stan and the rstan package to run the model in R. Model convergence has been assessed using R-hat and by inspecting traceplots. We applied post-stratification weights based on the target population's demographic structure (population size per age group and sex) to obtain seroprevalence estimates by estimating weighted means of probability of seropositivity based on the posterior distribution. Reported estimates are medians and 95% confidence intervals 2.5- and 97.5-quantiles of the resulting probability distributions.[2,25,26]

Furthermore, we determined the percentage of individuals in whom anti-spike IgG antibodies remained negative or positive (i.e. unchanged) or changed from negative to positive or positive to negative. We conducted all analyses in R, version 4.2.1.[27]

Results

Participation rate in March 2022 (Phase 5 of the Corona Immunitas research programme) was 18.1% in Ticino (850/4687) and 21.4% in Zurich (1044/4875). All participants were invited to take part in the Phase 6 blood sampling in June/July 2022, of whom 86.9% (739/850) in Ticino and 92.3% (964/1044) in Zurich decided to participate. Participation rate in Vaud in Phase 6 was 12.2% (850/6963).

Between 30 May and 11 July 2022 (Phase 6), we assessed in total 2553 cohort participants. Median age of participants of the three cantons was 49 years in Ticino [interquartile range (IQR) 35–64], 55 in Vaud (IQR 39–69) and 52 in Zurich (IQR 35–66). The percentage of female participants was 58.1% in Ticino, 55.9% in Vaud and 54.4% in Zurich. Most participants had received at least one dose of a SARS-CoV-2 vaccine (89.9% in Ticino, 91.1% in Vaud and 93.6% in Zurich). Around half of the study sample reported to have been infected recently, likely in 2022 (53% in Ticino, 48.7% in Vaud, 51.8% in Zurich) [Table 1 (stratified by canton); Supplementary Table S1, available as Supplementary data at *IJE* online (stratified by canton and age group)].

By June/July 2022, seroprevalence was estimated at 98.3% in Ticino [95% confidence interval (CI) 96.9–99.3%)], 98.4% in Vaud (95% CI 97.3–99.3%) and 98.9% in Zurich (95% CI 98–99.5%, Table 2). Anti-spike IgG antibodies were high across cantons and age groups (>90%). The percentage of individuals whose antibodies showed neutralization (ACE2r-blocking; functional capacity) was high against the ancestral strain (93.1% in Ticino, 93.9% in Vaud, 95.4% in Zurich) and Delta (90.7% in Ticino, 91.8% in Vaud, 90% in Zurich), and only slightly lower for the Omicron (84.3% in Ticino, 86.9% in Vaud, 83.6% in Zurich) variant of SARS-CoV-2, with no evident patterns across age groups and study sites.

From March 2022 to June/July 2022, the percentage of participants from Ticino and Zurich with detectable anti-spike IgG antibodies remained stable (>96% across age groups); only in seven participants the anti-spike IgG decreased below the threshold; all of these were unvaccinated and had become infected in 2022. In contrast, anti-nucleocapsid IgG antibodies fluctuated more and changed from positive to negative in 7.3% of the participants and from negative to positive in 18.6%. The neutralization capacity against the variants remained more stable (from positive to positive: 93.1% for the ancestral strain, 88.5% for Delta, and 80% for Omicron), with little variation across age groups [Figure 1 (overall trajectories), Supplementary Table S2, available as Supplementary data at *IJE* online (trajectories stratified by age group)]. There was a higher loss of neutralization capacity (from positive to negative) observed for Omicron with 8.6% (ancestral strain 1.2%, Delta 4.2%), whereas on the population level only little changed with respect to newly obtained neutralization capacity (from negative to positive: ancestral strain 1.3%, Delta 1.8%, Omicron 3.9%).

In June/July 2022, 1.0% (n = 25) of all participants were immune naïve (i.e. no detectable antibodies and no reported infection or SARS-CoV-2 vaccination), 41.1% (n = 1050) had vaccination-induced immunity only, 7.1% (n = 181) infection-induced immunity only, and 50.6% (n = 1289) hybrid immunity (vaccination and infection). For eight participants, relevant data to determine immune status were missing. Seroprevalence and hybrid immunity in Phases 5 and 6 of Corona Immunitas, in relation to the evolution of the pandemic in Switzerland, are illustrated in Figure 2. The percentage with high levels of

Table 1. Characteristics of the sample, Ticino, Vaud and Zurich, Switzerland, June–July 2022 ($n = 2553$), stratified by canton[a]

Characteristic	Ticino	Vaud	Zurich	All
Sample size	739	850	964	2553
Median age, years (IQR)	49 (35–64)	55 (39–69)	52 (35–66)	52 (36–66)
Age group, years				
16–29	128 (17.3%)	107 (12.6%)	156 (16.2%)	391 (15.3%)
30–44	186 (25.2%)	183 (21.5%)	235 (24.4%)	604 (23.7%)
45–64	241 (32.6%)	275 (32.4%)	306 (31.7%)	822 (32.2%)
65+	184 (24.9%)	285 (33.5%)	267 (27.7%)	736 (28.8%)
Female sex	429 (58.1%)	475 (55.9%)	524 (54.4%)	1428 (55.9%)
Education				
Primary	73 (9.9%)	73 (8.6%)	62 (6.4%)	208 (8.1%)
Secondary	409 (55.3%)	337 (39.6%)	394 (40.9%)	1140 (44.7%)
Tertiary	250 (33.8%)	426 (50.1%)	502 (52.1%)	1178 (46.1%)
Missing data	7 (0.9%)	14 (1.6%)	6 (0.6%)	27 (1.1%)
Household income, CHF/month[b]				
0–6000	317 (42.9%)	215 (25.3%)	320 (33.2%)	852 (33.4%)
6000–12 000	275 (37.2%)	349 (41.1%)	365 (37.9%)	989 (38.7%)
12 000–18 000	49 (6.6%)	159 (18.7%)	163 (16.9%)	371 (14.5%)
18 000+	40 (5.4%)	72 (8.5%)	70 (7.3%)	182 (7.1%)
Missing data	58 (7.8%)	55 (6.5%)	46 (4.8%)	159 (6.2%)
Working	453 (61.3%)	519 (61.1%)	666 (69.1%)	1638 (64.2%)
Missing data	3 (0.4%)	8 (0.9%)	6 (0.6%)	17 (0.7%)
Swiss citizen	590 (79.8%)	701 (82.5%)	823 (85.4%)	2114 (82.8%)
Missing data	1 (0.1%)	4 (0.5%)	4 (0.4%)	9 (0.4%)
Smoking	140 (18.9%)	159 (18.7%)	174 (18%)	473 (18.5%)
Missing data	2 (0.3%)	0	3 (0.3%)	5 (0.2%)
Obese (BMI $\geq$30 kg/m^2)	85 (11.5%)	108 (12.7%)	122 (12.7%)	315 (12.3%)
Missing data	0	0	0	0
Chronic disease[c]	165 (22.3%)	242 (28.5%)	268 (27.8%)	675 (26.4%)
Missing data	1 (0.1%)	0	0	1 (0%)
Assessment period				
First blood sample	2022-06-01	2022-05-30	2022-06-02	2022-05-30
Last blood sample	2022-06-25	2022-07-02	2022-07-11	2022-07-11
Anti-SARS-CoV-2 antibodies	723 (97.8%)	835 (98.2%)	954 (99%)	2512 (98.4%)
Known to be infected recently (NuC positive or positive test 2022)	392 (53%)	414 (48.7%)	499 (51.8%)	1305 (51.1%)
Missing data	0	3 (0.4%)	0	3 (0.1%)
Vaccinated ($\geq$1 dose)	664 (89.9%)	774 (91.1%)	902 (93.6%)	2340 (91.7%)
Missing data	4 (0.5%)	1 (0.1%)	2 (0.2%)	7 (0.3%)

BMI, body mass index; CHF, Swiss francs; IQR, interquartile range; NuC, nucleocapsid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Cantons (here Ticino, Vaud and Zurich) are federal states of the Swiss confederation.
[b] Mean exchange rate in June 2022: 1 Swiss franc = 1.03 euro/0.95 US dollar.
[c] Chronic disease includes reporting any of the following conditions: cancer, diabetes, diseases/treatments that weaken the immune system, physician-diagnosed high blood pressure, cardiovascular diseases and chronic respiratory diseases.

anti-spike IgG antibodies was more than double in persons with a hybrid immunity (99.8%) and vaccinated-only individuals (99%) compared with individuals with an infection only (45.9%) [Table 3 (pooled results); and Supplementary Table S3, available as Supplementary data at *IJE* online (results stratified by canton)]. Such large differences were also observed for neutralization capacity. Neutralization against Delta and Omicron was highest in participants with hybrid immunity, followed by those who had only been vaccinated and much lower in those with infection only (ancestral strain: hybrid 99.8%, vaccinated 98%, infected 47.5%; Delta: hybrid 99%, vaccinated 92.2%, infected 38.7%; Omicron: hybrid 96.4%, vaccinated 79.5%, infected 47.5%). Compared with March 2022 (Phase 5), hybrid immunity in participants from Ticino and Zurich increased from 35.8% to 50.6% by June/July 2022 (Phase 6), reflecting the high incidence with Omicron infections since spring 2022.

Discussion

This population-based cohort study showed that not only SARS-CoV-2 seroprevalence but also antibody titres were very high in the Swiss general population by June/July 2022, without notable differences across cantons, age or sex strata. At least 51% of participants developed hybrid immunity, and among those more than 96% had neutralizing antibodies against the ancestral strain, Delta and Omicron variants. In participants who received vaccination but were not infected previously, the percentage with neutralizing antibodies was lower, in particular against Omicron. The 7% of participants with only infection-induced immunity had about 15 times lower antibody titres and less than 50% of them showed neutralizing antibodies.

Trajectories of anti-spike IgG antibodies from March 2022 to June/July 2022 remained remarkably stable in participants from Ticino and Zurich. The fluctuation of anti-nucleocapsid IgG antibodies in contrast reflected quick waning of anti-nucleocapsid antibodies as well as substantial infection activity with the Omicron variant in spring 2022 in Switzerland. Thus, we observed stable seroprevalence and high levels of antibodies in the general population. Since the summer 2022 up to March 2023, the number of SARS-CoV-2 infections was still moderately high in Switzerland but fluctuated less

Table 2. Prevalence of SARS-CoV-2 IgG antibodies and ACE2r-blocking (neutralizing capacity) as measured by a virus-free assay, Ticino, Vaud and Zurich, Switzerland, June–July 2022, (n=2553), stratified by canton[a] and age group

	Ticino					Vaud					Zurich				
Prevalence	All	16–29 years	30–44 years	45–64 years	65+ years	All	16–29 years	30–44 years	45–64 years	65+ years	All	16–29 years	30–44 years	45–64 years	65+ years
Level of anti-spike IgG antibodies[b]															
Not detectable	18 (2.4%)	4 (3.1%)	3 (1.6%)	7 (2.9%)	4 (2.2%)	16 (1.9%)	NA	3 (1.6%)	9 (3.3%)	4 (1.4%)	12 (1.2%)	2 (1.3%)	5 (2.1%)	2 (0.7%)	3 (1.1%)
Low	8 (1.1%)	2 (1.6%)	3 (1.6%)	2 (0.8%)	1 (0.5%)	13 (1.5%)	2 (1.9%)	6 (3.3%)	3 (1.1%)	2 (0.7%)	10 (1%)	0	2 (0.9%)	4 (1.3%)	4 (1.5%)
Moderate	20 (2.7%)	6 (4.7%)	6 (3.2%)	4 (1.7%)	4 (2.2%)	24 (2.8%)	4 (3.7%)	6 (3.3%)	4 (1.5%)	10 (3.5%)	19 (2%)	3 (1.9%)	5 (2.1%)	9 (2.9%)	2 (0.7%)
High	693 (93.8%)	116 (90.6%)	174 (93.5%)	228 (94.6%)	175 (95.1%)	797 (93.8%)	101 (94.4%)	168 (91.8%)	259 (94.2%)	269 (94.4%)	923 (95.7%)	151 (96.8%)	223 (94.9%)	291 (95.1%)	258 (96.6%)
WHO U/mL, median (IQR)[c]	4505 (3279–6198)	4570 (3123–6588)	4485 (3182–5728)	4642 (3684–6298)	4417 (3393–5589)	4178 (3217–5334)	4120 (3057–5458)	4146 (3230–5140)	4172 (3187–5264)	4237 (3284–5558)	4224 (3245–5649)	4683 (3464–5587)	4017 (3170–5680)	4218 (3375–5491)	4310 (3308–5749)
Seroprevalence, % (95% CI)	98.3 (96.9–99.3)	97.4 (94.5–99)	99 (96.9–99.8)	98.3 (95.9–99.6)	98.6 (96.2–99.7)	98.4 (97.3–99.3)	98.2 (96.0–99.3)	98.9 (96.7–99.8)	98.1 (95.9–99.5)	99.0 (97.4–99.8)	98.9 (98.0–99.5)	98.4 (96.4–99.4)	98.8 (96.8–99.7)	99.5 (98.3–99.9)	99.1 (97.4–99.8)
Neutralization (≥50)															
Ancestral strain	688 (93.1%)	114 (89.1%)	173 (93.0%)	227 (94.2%)	174 (94.6%)	798 (93.9%)	101 (94.4%)	169 (92.3%)	259 (94.2%)	269 (94.4%)	920 (95.4%)	150 (96.2%)	222 (94.5%)	292 (95.4%)	256 (95.9%)
Delta	670 (90.7%)	110 (85.9%)	169 (90.9%)	221 (91.7%)	170 (92.4%)	780 (91.8%)	99 (92.5%)	163 (89.1%)	254 (92.4%)	264 (92.6%)	868 (90.0%)	148 (94.9%)	207 (88.1%)	278 (90.8%)	235 (88.0%)
Omicron	623 (84.3%)	107 (83.6%)	157 (84.4%)	208 (86.3%)	151 (82.1%)	739 (86.9%)	96 (89.7%)	157 (85.8%)	238 (86.5%)	248 (87.0%)	806 (83.6%)	140 (89.7%)	194 (82.6%)	260 (85.0%)	212 (79.4%)

ACE2r, angiotensin-converting enzyme 2 receptor; CI, confidence interval; IgG, immunoglobulin G; IQR, interquartile range; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO U/mL, World Health Organization units per millilitre (according to Elecsys ® Anti-SARS-CoV-2 S).

[a] Cantons (here Ticino, Vaud and Zurich) are federal states of the Swiss confederation.

[b] Unit for levels of anti-spike IgG antibodies is the median fluorescence intensity (MFI) as measured by the Luminex binding assay SenASTrIS (Sensitive Anti-SARS-CoV-2 Spike Trimer Immunoglobulin Serological).[20] Low: from threshold of test positivity to less than 3 standard deviations above this threshold (≥6 to <12); moderate: ≥3 standard deviations above positivity threshold but unlikely to provide neutralization (≥12 to <40); high: neutralizing capacity likely (≥40).

[c] The MFI values have additionally been translated to the U/mL scale as measured by the Elecsys Anti-SARS-CoV-2 immunoassay by Roche and are presented as population median and IQR.

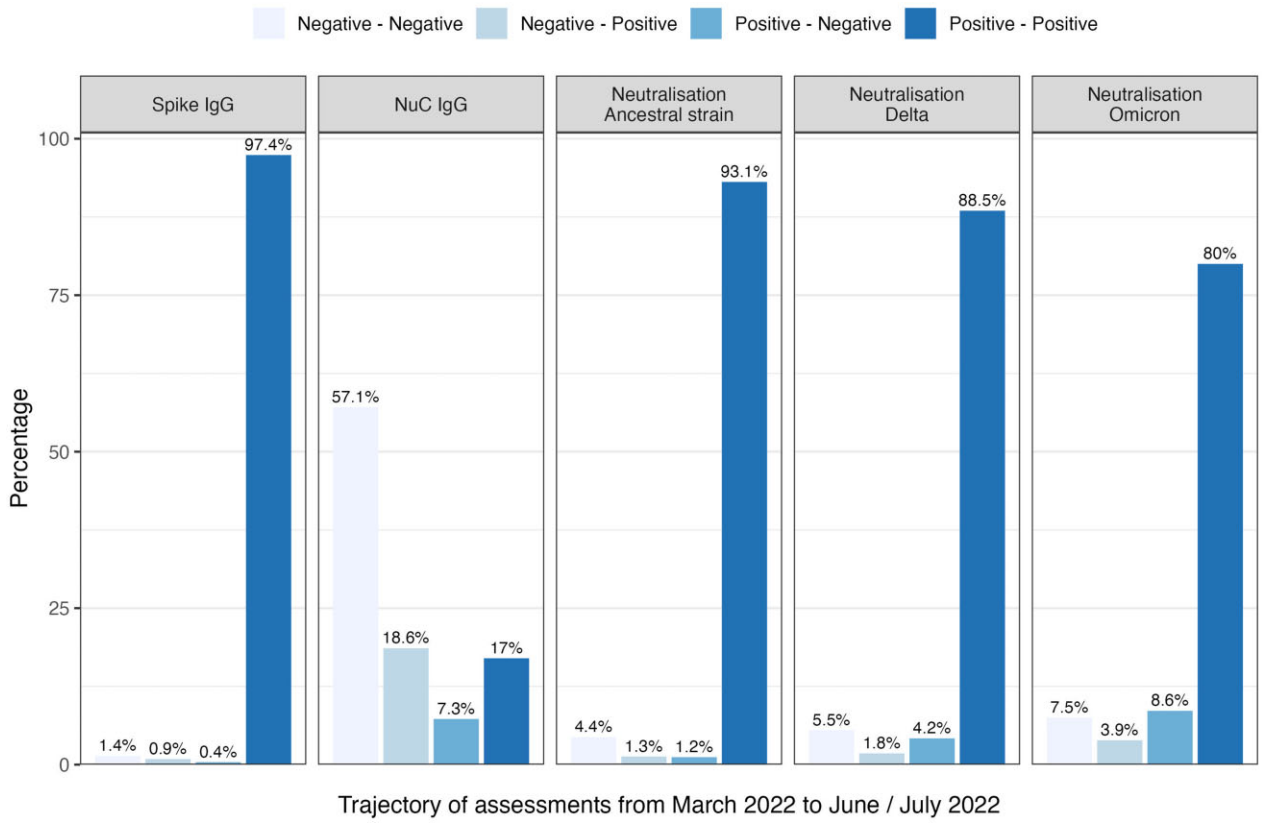

Figure 1. Trajectories of SARS-CoV-2 IgG antibodies and ACE2r-blocking (neutralizing activity) as measured by a virus-free assay, from March 2022 to June/July 2022. NuC, nucleocapsid; IgG, immunglobulin G. Seropositivity is defined based on the presence of anti-spike IgG antibodies according to the threshold of SenASTrIS test positivity with median fluorescence intensity (MFI) ≥6. Neutralization capacity based on virus-free assay with cut-off value of ≥50. Participants of Corona Immunitas from Ticino and Zurich, Switzerland ($n = 1702$)

than before and with very few hospital admissions due to COVID-19. Our results of stable and high population immunity together with the rather stable epidemiological situation imply that the transition from the pandemic to an endemic situation is taking place.

Our findings are in line with previous studies, mainly conducted in non-representative, convenience and relatively small samples, and/or in sub-populations (e.g. health care workers[28] and children),[29] showing that hybrid immunity confers higher immune protection and exhibits better neutralizing capacity compared with vaccine- and infection-induced immunity.[28–34] However, to our knowledge, this study is the first to demonstrate the extent of hybrid immunity and neutralization capacity in the general population in 2022.

A large study from Israel in 2021 showed that hybrid immunity provided stronger protection than vaccination and infection alone.[15] Although the proportion of persons with hybrid immunity was not reported, the observation time for persons with infection and vaccination up to (re-) infection or censoring was shorter compared with those only vaccinated or only infected, implying a very low prevalence of hybrid immunity back in 2021.

Strengths of our study include the prospective, population-based cohort study design, coverage of the three main language and cultural regions of a country, the well-established methods of the Corona Immunitas research programme, the large sample size and the use of previously validated serological tests and neutralizing antibodies.[21,24] In addition, retention of participants since March 2022 was high. Limitations include the modest participation rate, as is commonly the case in population-based studies; however, this may have introduced self-selection bias. We observed that in general, individuals with higher health literacy and trust in public health authorities in dealing with the pandemic were more likely to participate. Overall, this may have led to an overrepresentation of vaccinated persons and, consequently, of the seroprevalence. Another limitation is the lack of measures of cellular immunity, which is not feasible to test in large population-based studies. In addition, we may have underestimated hybrid immunity, as anti-nucleocapsid antibodies wane quickly and we likely missed some infections that occurred before 2022. Self-reports of infections compensate only to some extent for the low to moderate sensitivity of anti-nucleocapsid assays beyond 6 months of infection, because many infections are mild or asymptomatic. We assessed self-reported SARS-CoV-2 vaccination status and did not check vaccine certificates for feasibility reasons. Although we do not expect that many participants answered this question dishonestly or that recall bias occurred regarding vaccination, we cannot exclude this possibility. It is difficult to estimate how such a potential bias may have affected the results.

Our results have implications for vaccination strategies. Recommendations for primary series and booster vaccination need to consider the effectiveness and safety of vaccines as well as the epidemiological and societal context.[35] Seroprevalence is only a rough proxy marker of immunity in the population, since seropositive persons have a wide range of antibody titres and neutralizing capacity against SARS-

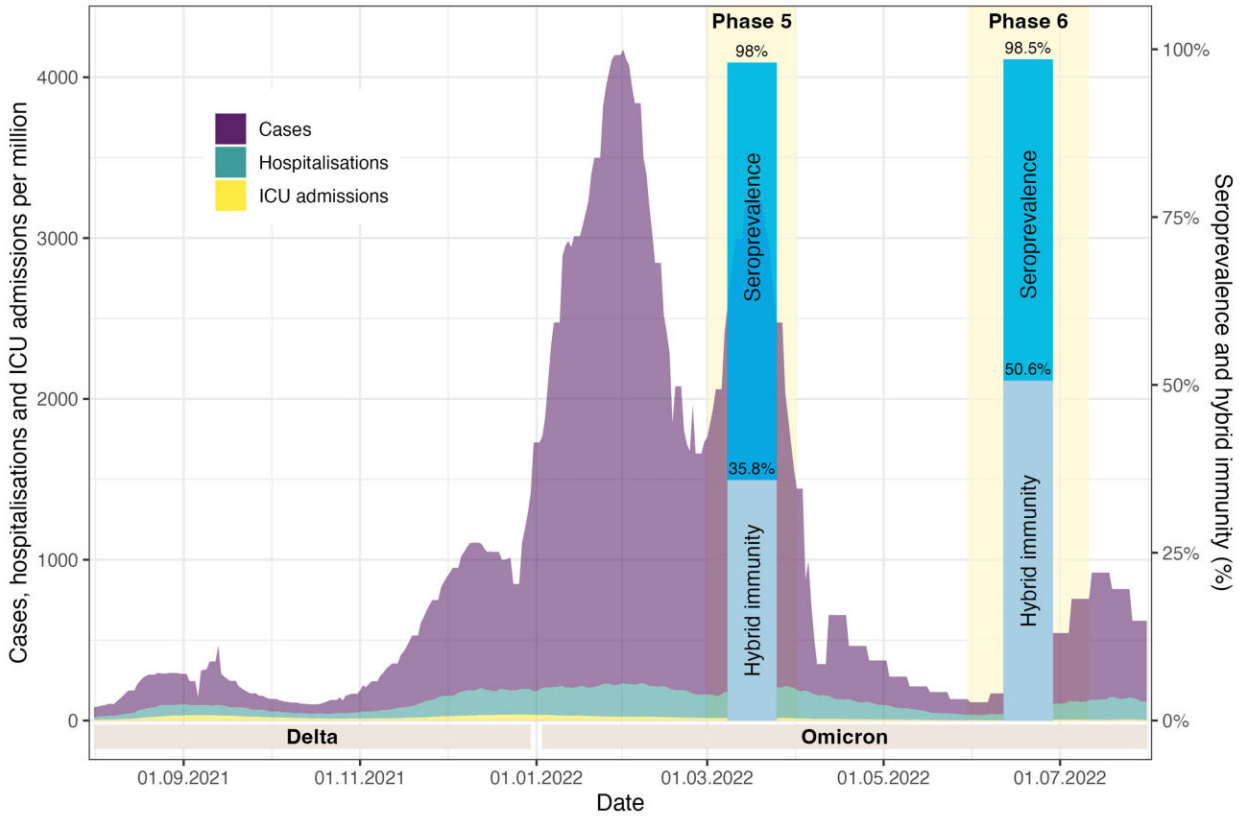

Figure 2. Seroprevalence and hybrid immunity in Phases 5 and 6 of Corona Immunitas, Switzerland, in relation to the evolution of the pandemic, August 2021–August 2022. ICU, intensive care unit. The evolution of the pandemic is visualized by the number of laboratory-confirmed SARS-CoV-2 cases (in purple), hospitalizations (turquoise) and intensive care unit admissions (in yellow) in Switzerland between August 2021 and August 2022, retrieved from: [https://ourworldindata.org/coronavirus].[37] The time frame of Phases 5 (March 2022, $n=1894$) and 6 (June/July 2022, $n=2553$) of Corona Immunitas, when the blood sampling and questionnaire assessments took place, are highlighted in light yellow. The results regarding seroprevalence and percentage of participants with hybrid immunity are visualized in dark and light blue bars, respectively

Table 3. Prevalence of SARS-CoV-2 IgG antibodies and ACE2r-blocking (neutralizing capacity) as measured by a virus-free assay, Ticino, Vaud and Zurich, Switzerland, pooled, June–July 2022, (n=2520[a]), stratified by vaccination and infection status of participants

Prevalence	Only vaccinated	Only infected	Vaccinated and infected
Sample size	1050	181	1289
Anti-spike IgG antibodies[b]			
Not detectable	0	17 (9.4%)	1 (0.1%)
Low	1 (0.1%)	30 (16.6%)	0
Moderate	10 (1%)	51 (28.2%)	1 (0.1%)
High	1039 (99%)	83 (45.9%)	1287 (99.8%)
WHO U/mL, median (IQR)[c]	4304 (3303–5716)	269 (34–1820)	4518 (3733–6005)
Anti-NuC IgG antibodies			
Not detectable	1050 (100%)	59 (32.6%)	522 (40.5%)
Low (≥6 to <12)	0	38 (21%)	407 (31.6%)
Moderate (≥12 to <40)	0	84 (46.4%)	360 (28%)
High (≥40)	0	0	0
Neutralization (≥50)			
Ancestral strain	1029 (98%)	86 (47.5%)	1287 (99.8%)
Delta	968 (92.2%)	70 (38.7%)	1276 (99%)
Omicron	835 (79.5%)	86 (47.5%)	1243 (96.4%)

ACE2r, angiotensin-converting enzyme 2 receptor; IgG, immunoglobulin G; IQR, interquartile range; NuC, nucleocapsid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO U/mL, World Health Organization units per millilitre (according to Elecsys ® Anti-SARS-CoV-2 S).

[a] Participants who were immunologically naïve ($n=25$) or were missing relevant data to determine their immune status ($n=8$) have been excluded.

[b] Unit for levels of anti-spike IgG antibodies is the median fluorescence intensity (MFI) as measured by the Luminex binding assay SenASTrIS (Sensitive Anti-SARS-CoV-2 Spike Trimer Immunoglobulin Serological).[20] Low: from threshold of test positivity to less than 3 standard deviations above this threshold (≥6 to <12); moderate: ≥3 standard deviations above positivity threshold but unlikely to provide neutralization (≥12 to <40); high: neutralizing capacity likely (≥40).

[c] The MFI values have additionally been translated to the U/mL scale as measured by the Elecsys Anti-SARS-CoV-2 immunoassay by Roche and are presented as population median and IQR.

CoV-2 VOCs as a consequence of infection only, vaccination only or both infection and vaccination, as this study and other studies showed.[13,14] Therefore, information on the proportion of persons in the general population with neutralizing capacity and hybrid immunity provides more solid guidance. The Swiss Federal Vaccination Commission recently released finely granulated recommendations for booster and primary series vaccinations, based on the best available international evidence on the effectiveness and safety of bivalent or other booster vaccines and based on the results of Corona Immunitas presented here. Whereas the Commission issued a strong recommendation for a second booster for people above 64 years of age, for those with chronic conditions and for pregnant women, the recommendation was moderately strong for health care staff and formal and informal caregivers, and only weak for the general population between 16 and 64 years of age. In addition, they recommended only one primary series dose for unvaccinated persons since most of them have had a SARS-CoV-2 infection (>90% according to the results presented here). These recommendations considered the high seroprevalence in Switzerland and the high proportion of persons with hybrid immunity and neutralizing capacity and include considerations on the optimal timing for the next booster campaign in autumn/winter 2022. The Canadian authorities issued similar recommendations for booster vaccines but population-based data on immunity in the population were not available to the extent and level of detail presented here.[36]

Conclusion

This prospective population-based cohort study with 2553 participants showed that seroprevalence remained very high in Switzerland in 2022, without differences across cantons and age groups. Antibody titres increased, and the majority of participants developed hybrid immunity with very high levels of neutralization against the ancestral strain, Delta and Omicron variants of SARS-CoV-2. Individuals with immunity only from infection had 15 times lower antibody titres, and less than half of them showed neutralization. Our results support the emerging recommendations of some countries where booster vaccinations are still strongly recommended for vulnerable persons but less strongly recommended for individuals in the general population.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the responsible ethics committees of the cantons of Zurich (first approval 28 May 2020, BASEC Registration No 2020–01247), Ticino (first approval 23 June 2020, BASEC Registration No 2020–01514) and Vaud (first approval 23 April 2020, BASEC No 2020–00887), Switzerland. Written informed consent was obtained from all individual participants included in this study.

Data availability

De-identified individual participant data underlying the findings and the used codes of this study will be available for researchers. Requests can be made to the Executive Committee of Corona Immunitas [https://zenodo.org/record/7520125] or to the corresponding author.

Supplementary data

Supplementary data are available at *IJE* online.

Authors contributions

M.A.P., E.A., J.S.F., A.F., M.K., M.B., V.D.A. and R.A. conceptualized and designed this study. A.F., R.A., A.B.D., J.V., M.K., V.V.W. and A.M.A. contributed to the acquisition of the data. M.K. prepared the analytical datasets, conducted the statistical analyses and drafted the figures. C.P. and G.P. contributed to the laboratory analyses. R.A., A.M.A. and .EA. conducted a systematic literature search. M.A.P. and J.S.F. obtained funding. All authors had full access to the data and contributed to the interpretation of the findings. M.A.P., A.F., M.K. and R.A. drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors accept full responsibility for the content of the paper and have seen and approved the final version. A.F., M.K. and R.A. contributed equally to this study. M.A.P. is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflict of interest

None declared.

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