SEROPREVALENCE STUDIES IN THE ALBANIAN POPULATION: FOLLOWING THE MARCH TOWARD HERD IMMUNITY (2020-2023)

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ABSTRACT

The COVID-19 pandemic posed significant public health challenges, particularly in understanding SARS-CoV-2 transmission dynamics and the development of population-level immunity. The present study presents a comprehensive report on the seroprevalence of IgG anti-SARS-CoV-2 antibodies in the Albanian population from 2020 to 2023, offering insights into immunity progression and the impact of vaccination. The study involved five rounds of cross-sectional serosurveys conducted in adults aged 18 to 70 years in Tirana, Albania, during key pandemic periods: June 2020, December 2020, August 2021, August 2022, and April 2023. Participants were randomly selected from five primary health centres, with sample sizes ranging from 164 to 2,025 across rounds. Serological testing was performed using enzyme-linked immunosorbent assays (ELISA) to detect IgG antibodies against SARS-CoV-2 spike (S1) and nucleoprotein (N) antigens. Seropositivity rates and antibody levels were evaluated, and vaccination data were collected through standardized questionnaires. The seroprevalence of anti-S1 antibodies increased from 7.5% in June 2020 to 48.2% in December 2020, reflecting the rapid spread of COVID-19. By August 2021, seroprevalence had risen to 71.7%; by August 2022, it reached

93.1%. The study also identified a significant rise in hybrid immunity, with the proportion of vaccinated individuals who had also been infected increasing from 19.9% in August 2021 to 56.0% in August 2022. In 2022, anti-S1 antibody levels were 2.4 times higher than in 2021, indicating that both vaccination and natural infection contributed to population-level immunity. The findings suggest that the Albanian population may have reached herd immunity by late 2022, primarily due to widespread hybrid immunity. Nonetheless, ongoing vaccination efforts—particularly among high-risk groups such as the elderly and immunocompromised— remain essential. This study provides a foundation for long-term monitoring of SARS-CoV-2 seroprevalence in Albania and offers valuable insights for future vaccination strategies in similar settings.

***Keywords**:* COVID -19, Albanian population, herd, immunity

1. INTRODUCTION

The COVID-19 pandemic posed unprecedented challenges to global public health, particularly in elucidating SARS-CoV-2 transmission dynamics and the development of immunity in populations (Filip *et al*., 2022; Liu *et al*., 2024). Accurate estimation of true infection prevalence has been vital for tracking epidemiological trends, informing public health strategies, and evaluating the effectiveness of preventive measures (Ibrahim 2020; Xiang *et al*., 2021). Although molecular and antigen testing provide crucial information on active cases, these methods often underdetect asymptomatic or mildly symptomatic cases, leading to an incomplete picture of viral spread (Robinson *et al*., 2022). Seroprevalence studies, which quantify the proportion of individuals with SARS-CoV-2 –specific antibodies, have revealed the broader scope of infection and immunity (Bergi *et al*., 2022; Sarkar *et al*., 2022). Such investigations offer key insights into viral transmission patterns and the development of immunity, whether derived from natural infection or vaccination (ECDPD 2021; Merkt *et al*., 2024). A critical area of research has been the interplay between vaccine-induced and naturally acquired immunity, underscoring their roles in optimizing vaccination strategies (Subbarao *et al*., 2021; Gazit 2022). The balance between these two immunity sources has varied across countries and populations, shaped by vaccine availability, the intensity of immunization campaigns, and the extent of viral exposure within communities (Castro *et al*., 2021; Mongin *et al*., 2023).

The pandemic significantly affected Albania, a middle-income country in Eastern Europe. Since early 2020, national efforts have focused on understanding the immune response to SARS-CoV-2 within the Albanian

population, particularly the progression of seropositivity throughout the pandemic (Sulcebe *et al*., 2023 (a), (b); Cenko *et. al*., 2022). While global studies have extensively explored SARS-CoV-2 seroprevalence, few have longitudinally tracked it across multiple time points in a single population, spanning from the early stages of the pandemic to the later phases (Bergeri *et al*., 2022; Karkanista *et al*., 2023; Carreño *et al*., 2024). This paper analyses humoral immune responses to SARS-CoV-2—specifically, antibodies targeting Spike-1 (S-1) and nucleoprotein (N) antigens— in relation to vaccination and prior infection, across five serosurveys conducted between May-June 2020 and January-March 2023. The consolidated analysis of these serosurveys traces the progression toward herd immunity in the Albanian population over the three years of the pandemic, providing insights that are highly relevant for shaping future public health strategies and vaccination efforts, particularly in middle-income settings.

2. MATERIALS AND METHODS

Study Design and Population

This cross-sectional observational cohort study was conducted in accordance with the STROBE guidelines (von Elm *et al*., 2008). Participants were randomly selected to ensure a representative sample of the adult Albanian population. Five consecutive cross-sectional serosurveys were carried out between 2020 and 2023 to assess the seroprevalence of SARS-CoV-2 antibodies over time. The target population included adults aged 18 years or older, randomly chosen from the electronic registries of five primary health centres (PHCs) in Tirana and Berat, which collectively serve approximately 281,600 residents. The sampling strategy was designed to ensure adequate representation across different age groups and geographic areas within the urban Albanian population.

Sampling Methodology

A systematic, multi-stage sampling approach was employed in all serosurveys to enhance the generalizability of the results. Initially, four Primary Health Centres (PHCs) in Tirana and one in Berat were randomly selected to represent the urban population in two different Albanian cities. Physicians and head nurses at these centres were instructed to randomly

choose unrelated individuals from electronic family doctor registries, which maintain up-to-date records of residents within their service areas.

For the 2020 serosurvey, two rounds of sampling were conducted: the first in June and the second in December, with target sample sizes of 300 and 900 adults aged 18 years or older, respectively. In the 2021 and 2022 surveys, independent samples were drawn during July-August. The final serosurvey, conducted between January and April 2023, included 164 adults aged over 18 years. The sample sizes of individuals in the 2020 samples were determined by the availability of serological testing kits, while the smaller sample size in 2023 round was due to the concurrent investigation of cellular immune responses to SARS-CoV-2 (Sulcebe *et al*., 2025). Participants were contacted by phone and invited to health centres for blood sample collection and interviews. Prior to enrolment, written informed consent was obtained from all participants. A standardized questionnaire was administered to collect demographic data, health status, history of COVID-19 infection, and vaccination information.

Serological Testing

The laboratory work was conducted at the Research Centre for Biotechnology and Genetics of the Albanian Academy of Sciences. Serological testing was performed using enzyme-linked immunosorbent assay (ELISA) to detect IgG antibodies against the SARS-CoV-2 Spike-1 (S1) and Nucleoprotein (N) antigens. Two commercially available diagnostic kits from Euroimmun (Luebeck, Germany) were used across the surveys: the IgG Anti-S1-SARS-CoV-2 ELISA and the IgG Anti-NCP-SARS-CoV-2 ELISA, with reported sensitivities of 94.4% and 94.6%, and specificities of 99.6% and 99.8%, respectively. Anti-NCP IgG antibodies were measured only in the third, fourth, and fifth rounds of the study.

Blood samples were transported to the laboratory within three hours of collection. ELISA results were evaluated by calculating the optical density ratio of the sample to the calibrator (Index Ratio, IR). Samples with an IR greater than 1.1 were classified as seropositive, those between 0.8 and 1.1 as borderline, and those below 0.8 as negative. Only samples with an IR above 1.1 were included in the seropositivity analysis. The ELISA kits were internally validated at the Research Centre of Biotechnology and Genetics using reference panels of pre-pandemic negative sera. Batch-level quality control was maintained throughout all testing phases, ensuring sensitivity greater than 94% and specificity exceeding 99%.

Statistical Analysis

The primary outcomes were seropositivity rates and IgG anti-S1 and anti-N antibody levels. Categorical variables, such as seropositivity and response rates, were analysed using chi-square or Fisher's exact tests. Depending on data distribution, continuous variables, including antibody levels, were analysed using Student's t-test or the Mann-Whitney U test. A significance level of 0.05 was applied to all statistical tests. Statistical analyses were performed using MedCalc® Statistical Software version 20.210 and IBM SPSS Statistics version 24.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of the Albanian Academy of Sciences (Project number 33-07-05-2020). Before their inclusion in each survey, all participants provided written informed consent. The study adhered to the ethical principles of the Declaration of Helsinki.

Results Demographics and Clinical Data on Previous COVID-19 Infection and Vaccination

Table 1 summarizes the key demographic characteristics, previous SARS-CoV-2 infections, and vaccination data across the five rounds of serosurveys. In the first round, conducted between June 27 and July 3, 2020, 266 participants were enrolled, with a median age of 48.0 years (range: 20–77 years). The second round, held from December 21 to 28, 2020, included 817 additional participants with a median age of 49.0 years (range: 20–85 years). In the third round (July–August 2021), 1,955 individuals participated, with a median age of 48 years (range: 18–97 years). The fourth serosurvey conducted in July–August 2022, involved 2,025 individuals (median age: 48 years, range: 18–87 years). In the final round conducted between January 23 and April 3, 2023, 164 participants were enrolled, with a median age of 43 years (range: 18–70 years). The proportion of female participants varied across the rounds, from 72.2% in June 2020 to 54.7% in April 2023.

The self-reported rate of previous COVID-19 infection increased from 27.0% in June 2020 to approximately 50.0% in December 2020 and August 2021. Between 2021 and 2022, an additional 11.7% increase was observed, reaching a plateau of around 60% by April 2023.

Vaccination coverage was reported at 43.5% in August 2021, rising to 68.9% in August 2022 and 62.5% in April 2023. The proportion of individuals with hybrid immunity (i.e., both vaccinated and previously infected) increased from 19.9% in August 2021 to 56.0% in August 2022, followed by a modest decrease to 51.2% in April 2023 (Table 1).

Table 1. Main demographic and clinical characteristics of the sample populations studied in different rounds of the study

Year	Nr. of individuals studied	Sex (% females; 95% CI)	Age (Years; median; 95% CI)	Individuals with reported previous Covid (+) (%; 95% CI)	Vaccine (+) Individuals (%; 95% CI)	Covid (+) and Vaccine (+) Individuals (%; 95% CI)
June 2020	269	72.2% (66.4 - 77.5)	48.0 (45.0 - 50.0)	27.0 % (21.5 - 32.9)	N.A.	NA
Statistical Significance (*P* value)	_	0,0109	NS	< 0.0001	_	_
December 2020	815	63.7% (60.3 - 67.0)	49.0 (45.8 - 52.7)	50.4 % (46.9 - 53.9)	NA	NA
Statistical Significance (*P* value)	_	NS	NS	NS	_	_
August 2021	1955	59.4% (57.2 - 61.4)	48.0 (47.0 - 49.0)	49.9 % (47.6 - 52.2)	43.5 % (41.1 - 45.9)	19.9% (18.1-21.9)
Statistical Significance (*P* value)	_	NS	NS	< 0.0001	< 0.0001	< 0.0001
August 2022	2025	59.9% (57.8 - 61.9)	48.0 (47.0-50.0)	61.6 % (59.3 - 63.7)	68.9 % (66.8 - 70.9)	56.0 % (53.9-58.2)
Statistical Significance (*P* value)	_	NS	NS	NS	NS	NS
April 2023	164	54.7% (46.7 - 62.5)	43.0 (37.1 - 46.9)	59.8 % (52.1 - 67.9)	62.5 % (55.6 - 67.5)	51.2 % (46.7 -57.1)

NA: Non-Available; NS: Non-Significant

Anti-S1-IgG and Anti-N-IgG Seropositivity and Antibody Levels (June 2020–April 2023)

In a control group of 100 pre-pandemic serum samples collected randomly from the Blood Bank's frozen sera archive of 2018, 2% tested positive for anti-S1-IgG antibodies. These samples were subsequently confirmed positive for anti-N-IgG antibodies using two independent diagnostic kits.

In the first round (June 2020), the seropositivity rate for anti-S1-IgG antibodies was 7.5%, which surged to 48.2% by December 2020—representing a sixfold increase. This upward trend was consistent across different health centres, age groups, and sexes, with no significant differences observed between males and females. By August 2021, the seropositivity rate had reached 71.7%; rising further to 93.1% by August 2022. Additionally, in 2022, the median level of anti-S1-IgG antibody was 2.3 times higher than in 2021 ($p < 0.0001$, Table 2).

Table 2. Anti-S1-IgG and Anti-N-IgG Seropositivity Rates and Antibody Levels Across all Serosurvey Rounds from June 2020 to April 2023**.**

Serosurvey Studies	Anti-S1-IgG Rates (%)	Anti-S1-IgG Levels (IR) medians and 95% CI)	Anti-N-IgG Rates (%)	Anti-N-IgG Levels (IR medians and 95% CI)
June 2020	7.5% (4.7 - 11.3)	0.35 (0.21 - 0.42)	_	_
Statistical Significance (*P* value)	< 0.0001	< 0.0001	_	_
December 2020	48.2% (44.7 - 51.7)	0.93 (0.55 - 1.26)	_	_
Statistical Significance (*P* value)	< 0.0001	< 0.0001	_	_
August 2021	71.7 % (69.9 - 73.7)	2.97 (2.75 - 3.21)	39.6 % (37.3 - 41.9)	0.74 (0.66 - 0.80)
Statistical Significance (*P* value)	< 0.0001	< 0.0001	< 0.0001	< 0.0001
August 2022	93.1 % (91.9 - 94.2)	6.90 (6.70 - 7.00)	62.6 % (60.4 - 64.7)	1.67 (1.58 - 1.80)

Statistical Significance (*P* value)	NS	NS	< 0.0001	< 0.0001
April 2023	93.3 % (88.3 - 96.6)	7.01 (6.51-7.49)	40.9 % (33.3 - 48.9)	0.91 (0.78 - 1.07)

NS: Non-Significant

For anti-N-IgG antibodies, seropositivity rates were consistently lower than those observed for anti-S1-IgG. In August 2021, the anti-N-IgG seropositivity rate was 39.6%, which increased to 62.6% in 2022—representing a 1.58-fold increase. However, by April 2023, the rate had declined to 40.9% ($p < 0.0001$, Table 2). Figures 1 and 2 illustrate the trends in seropositivity and antibody levels for both anti-S1-IgG and anti-N-IgG across all survey rounds.

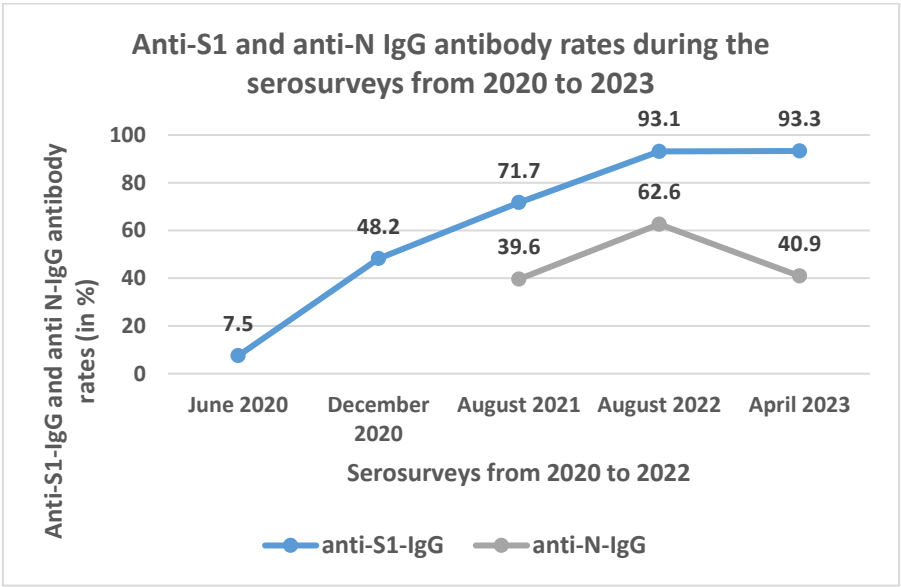

Fig.1: Seroprevalence rates (in %) of anti-S1-IgG and anti-N-IgG antibodies across all rounds of the serosurvey.

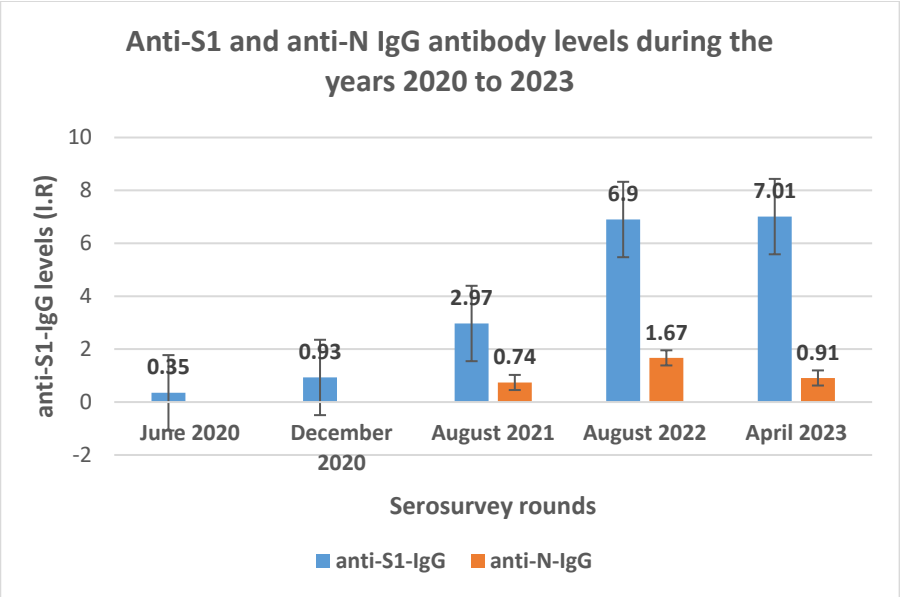

Fig. 2: Quantitative levels (medians) of anti-S1-IgG and anti-N-IgG antibodies across all rounds of the serosurvey.

The proportion of asymptomatic seropositive individuals — defined as unvaccinated with no reported history of COVID-19 who nonetheless tested positive for anti-S1-IgG antibodies— ranged from a peak of 45.0% in June 2020 to a low of 33.9% in August 2021. No statistically significant differences were observed between cohorts across survey rounds (Table 3).

Table 3. Percentage of Asymptomatic Individuals by Different Serosurveys from 2020 to 2023.

	Percentage of asymptomatic* individuals (95% CI)
June 2020	45.0 % (23.1 - 68.5)
December 2020	38.4 % (33.6 - 43.4)
August 2021	33.9 % (28.2 - 35.8)

August 2022	36.2 % (31.2 - 41.5)
April 2023	37.7 % (35.4 - 39.9)

*Asymptomatic individuals are calculated as the ratio of S1-IgG (+) Covid (-) Vaccine (-) individuals to all S1-IgG (+) Vaccine (-) (%; 95% CI) individuals

3. DISCUSSIONS

This study provides a detailed analysis of immune response dynamics to SARS-CoV-2 in the Albanian population from spring 2020 to spring 2023. It focuses on the seroprevalence of IgG anti-S1 antibodies among individuals aged 18 to 70 years in Tirana, capturing the evolution of population-level immunity from the onset of the pandemic to its transition to endemicity.

The study was conducted in five distinct rounds, each corresponding to key epidemiological phases: June 2020 (end of the first wave), December 2020 (Alpha variant peak), August 2021 (transition to Delta), August 2022 (Omicron peak), and January–April 2023 (endemic phase). A consistent methodology was employed across all rounds to assess antibody responses to both the SARS-CoV-2 spike and nucleoprotein antigens.

Comparative studies from Europe and the United States show variable seroprevalence rates, influenced by factors such as urban density, public health interventions, and the stage of the pandemic (Natale *et al*., 2023). In Albania, seroprevalence increased from 7.5% in June 2020 to 48.2% in December 2020, reflecting a significant surge in COVID-19 cases. Similar trends were reported in other Eastern European countries during the same period such as Bosnia-Herzegovina (40.4%) and Georgia (51.3%) (Natale *et al*., 2023). In contrast, Eastern European countries like the United Kingdom and Sweden showed more modest increases, ranging from 6–9% and 5.2–7.9%, respectively (Vaughan *et al*., 2023, Office for National Statistics 2021). The rapid rise in Albanian cases is likely attributable to factors such as relaxed social distancing and high population susceptibility (Shafer *et al*., 2021; Taylor *et al*., 2023).

Our findings also highlight the high prevalence of asymptomatic infections, with 38.4% to 45% of seropositive individuals reporting no COVID-19-like symptoms. These rates align with global estimates, which suggest that asymptomatic infections comprise between 9.2% and 69% (Kronbischler *et al*., 2020; Chen *et al*., 2021; Ma *et al*., 2021).

The study also revealed an overrepresentation of women in the first two rounds, likely reflecting men's lower utilization of public health services—an observation consistent with findings from other studies (IPH 2019; Boggiannidou *et al*., 2020).

Additionally, the infection-to-case ratio in Tirana was estimated to exceed 10:1 by December 2020, indicating significant underreporting of cases. This estimate aligns with broader findings, where a median ratio of 18.1infections per confirmed cases has been reported globally (Bobrovitz *et al*., 2021).

By August 2021, seroprevalence in the Albanian population reached 71.7%. A systematic meta-analysis reported a global seroprevalence of 59.2% from infection or vaccination September 2021 (Frei *et al*., 2023).

Despite high seroprevalence in August 2021, SARS-CoV-2 continued to spread during subsequent Delta and Omicron waves. However, by August 2022— coinciding with the decline of the Omicron surge— seroprevalence had increased to 93.1%, and antibody levels were 2.4 times higher than in 2021. This reflects the cumulative effects on both natural infection and vaccination and likely contributed to stabilization of transmission, with no significant epidemic surges observed thereafter.

Our data demonstrate a high prevalence of hybrid immunity, which provides more robust and durable protection compared to immunity from natural infection or vaccination alone (Lasrado *et al*., 2023: Frei *et al*., 2023 Zaballa *et al*., 2023). By late 2022, over 96% of adults in many regions —including the United States— had developed SARS-CoV-2 antibodies through infection, vaccination, or both, with nearly half exhibiting hybrid immunity (Tunheim *et al*., 2022; Jones *et al*., 2023..

This study has several limitations. The sample size in the first, second and fifth rounds were relatively small, and the sample may be biased by the overrepresentation of women and individuals more likely to access public health services. Moreover, the findings primarily reflect the urban populations of Tirana and Berat and many not be generalized to rural areas, where the population density is lower interaction patterns differ.

In conclusion, this study underscores the combined role of vaccination and natural infection in achieving high levels of population immunity in

Albania. By August 2022 and April 2023, the observed seroprevalence of approximately 93% suggests Albania may have approached the threshold for herd immunity, largely driven by hybrid immunity. Continued vaccination efforts, particularly targeting immunocompromised and elderly individuals, remain essential for maintaining protective population-level immunity. Furthermore, the study provides a foundation for seroprevalence and informs future vaccination strategies in Albania and comparable settings.

Overall, the findings emphasize the critical role of hybrid immunity in sustaining population immunity and suggest that while a single booster may suffice for the general population, additional doses may be warranted for high-risk groups.

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