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Evolution of Anti-SARS-CoV-2 Humoral Immunity Following COVID-19 Infection among Vaccinated and Previously Infected Healthcare Workers in Côte d'Ivoire

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Abstract

Background: Coronavirus disease (or COVID-19), caused by the novel coronavirus SARS-CoV-2, the most virulent identified to date, remains a major global public health challenge. Given the essential role of specific anti-SARS-CoV-2 humoral immunity in protection against reinfection, it is crucial to characterize its kinetics to adapt vaccination strategies. This longitudinal study aimed to evaluate the kinetics of anti-SARS-CoV-2 IgG and neutralizing antibodies produced by previously immunized subjects in response to new infection over 28 days within a cohort of 36 healthcare workers diagnosed with COVID-19 in Côte d'Ivoire. **Methods:** Between April and June 2022, healthcare professionals infected with COVID-19 were recruited from three university hospitals in Abidjan. Serum samples were collected, and anti-Spike IgG and neutralizing antibodies were quantified using a competitive enzyme immunoassay (Chorus TRIO, DIESSE). Both antibody types were evaluated at days 0, 7, 14, 21, and 28 following diagnosis. **Results:** IgG levels increased significantly over time ($p < 0.0001$), whereas neutralizing antibodies showed no significant variation. At diagnosis, residual IgG titres were higher in previously infected individuals, while neutralizing antibody levels were higher among vaccinated subjects and those with hybrid immunity. Upon reinfection, antibody production was enhanced in these groups. The higher IgG levels in previously infected individuals compared to vaccinated ones suggest a stronger booster effect when the same mode of immunization is maintained. Overall, IgG levels tended to rise progressively, contrasting with a decline in neutralizing antibodies, which typically occurred after a peak at day 14. **Conclusion:** IgG levels gradually increased, while neutralizing antibody titres declined after peaking on day 14.

Keywords

Neutralizing Antibodies, COVID-19, IgG, Healthcare Workers, SARS-CoV-2

1. Introduction

Coronavirus disease (COVID-19), caused by the novel and highly virulent coronavirus SARS-CoV-2 [1], remains a global public health concern. Declared a pandemic by WHO on 11 March 2020, control efforts have relied heavily on vaccination programmes. Many individuals have also acquired natural immunity following infection and recovery. Understanding immune responses, particularly humoral immunity, is critical for characterizing disease pathogenesis. Humoral immunity plays a major role in protection against reinfection [2]. Despite acquired immunity, reinfection cases have been documented globally [3] [4]. The decline of antibodies induced by natural infection has thus become a worldwide concern, particularly with emerging SARS-CoV-2 variants. Longitudinal studies of immune responses after infection and the characterization of long-term antibody responses are crucial to estimate the immunological effects of vaccination and determine the need for booster doses. The duration and persistence of antibody responses to SARS-CoV-2 are currently the subject of numerous studies, particularly in light of the recent approvals of vaccines against this virus [5] [6]. Several studies have highlighted the sustained presence of IgG in patients cured of SARS-CoV-2 for more than two years [7] [8], underlining the importance of monitoring not just the persistence of anti-SARS-CoV-2 antibodies over time, but also their evolution. Studying the kinetics of these antibodies has also enabled the definition of booster vaccination, which is linked to, and determined by, epidemiological scenarios including variants of concern. According to the WHO, a third dose (booster) could, in the short term, fully or partially restore vaccine efficacy [9]. As humoral immunity plays an important role in protection against reinfection, studying the kinetics of antibodies during reinfection in people who have already been immunized through vaccination, previous infection, or a combination of both (known as 'hybrid immunity'), could help us assess the appropriateness of this third dose. Furthermore, no study has yet been conducted in sub-Saharan Africa investigating the kinetics of anti-SARS-CoV-2 antibodies in previously immunized patients. This study aimed to assess the kinetics of antibody responses produced by immunized subjects in response to a new SARS-CoV-2 infection over a 28-day period.

2. Materials and Methods

Study Design and Patient Recruitment

This was a longitudinal analytical study conducted over a six-month period between April and September 2022. A cohort of 36 healthcare professionals infected with SARS-CoV-2 was recruited from the three operational University Teaching Hospitals (CHUs) in Abidjan (Cocody, Angre, and Treichville) and monitored for 28 days. All participants provided blood samples, and the resulting serum was used for serological assays to monitor the evolution of anti-SARS-CoV-2 antibodies. All healthcare personnel with SARS-CoV-2 infection confirmed by RT-qPCR were included in the study, regardless of sex, infection history, or vaccination status. Sociodemographic and medical history data were collected using a structured questionnaire, including comorbidities, COVID-19 vaccination history (verified through vaccination cards), and prior SARS-CoV-2 infections. Regarding disease severity, asymptomatic cases were classified as simple COVID-19, those with mild symptoms as mild cases, those with evident symptoms as moderate, and those requiring hospitalization as severe cases.

The study was conducted following approval and authorization from the National Ethics Committee of Côte d'Ivoire. All participants provided written informed consent. Confidentiality was maintained throughout the study through anonymized data coding.

Sample Collection and Transport

All participants underwent nasopharyngeal and blood sampling. The initial nasopharyngeal swabs were used for antigen testing performed in the presence of the participants. If the antigen test was positive, a confirmatory RT-qPCR was carried out at the Immunology and Allergology Laboratory of the Faculty of Medical Sciences, Abidjan (SMA). Venous blood samples were collected from the antecubital vein into dry tubes for quantification of IgG and neutralizing antibodies (nAbs). Initially planned for a 60-day follow-up, the high cost and shortage of diagnostic tests during the study period led us to follow participants for only 28 days, with visits scheduled on days 7, 14, 21, and 28, during which nasopharyngeal and blood samples were taken. Nasopharyngeal swabs were placed in viral transport medium (VTM), while blood samples were kept in primary tubes. All samples were transported in cool boxes at 4˚C to the aforementioned laboratory for analysis. Blood samples were centrifuged at 3000 rpm for 5 minutes in refrigerated centrifuges, and sera were aliquoted for analysis. In cases where analyses were delayed, nasopharyngeal and serum samples were stored at −80˚C for a maximum of seven days.

Sample Analysis

COVID-19 diagnosis was initially established using STANDARD Q COVID-19 Ag rapid tests (SD BIOSENSOR, Republic of Korea), following the manufacturer's protocol. Positive results were confirmed using real-time PCR (RT-qPCR), targeting two conserved viral genes: the nucleocapsid (N) gene and the RNA-dependent RNA polymerase (RdRp) gene of SARS-CoV-2. RNA extraction was performed using the KingFisher™ Duo Prime system (Thermo Fisher Scientific) with the MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit (Applied Biosystems, USA). Amplification of extracted RNA was conducted using the CFX96 Real-Time PCR Detection System (Bio-Rad, USA) according to the manufacturer's protocol. Samples were considered positive when amplification occurred for both targets, with a threshold cycle (Ct) value below 35.

Quantification of anti-COVID-19 antibodies was performed using a competitive enzyme-linked immunosorbent assay (Chorus SARS-CoV-2 'Neutralizing' Ab, DIESSE, Italy), which is a surrogate assay that measures binding inhibition for the quantitative determination of total anti-S1 SARS-CoV-2 neutralizing antibodies and IgG. Analyses were carried out on disposable cartridges using the Chorus TRIO platform. Results were expressed in Binding Antibody Units per milliliter (BAU/ml) following WHO recommendations for anti-SARS-CoV-2 antibody reporting. Results ≥ 50 BAU/ml were considered positive, while those < 20 BAU/ml were negative. In total, 180 serum and 180 nasopharyngeal samples were analyzed.

Data Processing and Statistical Analysis

Data entry and table generation were performed using Microsoft Word and Excel 2016. Statistical analyses and graphical representations were conducted using GraphPad Prism 8.0.2 version. As quantitative data were not normally distributed, results were expressed as means or medians, standard deviations, minimum and maximum values, and qualitative variables as proportions. Median comparisons were performed using the Kruskal-Wallis test (ANOVA) with a significance threshold of 5%. Spearman's rank correlation test (two-tailed) was used to assess correlations.

3. Results

Patient Characteristics

During this longitudinal study, a cohort of 36 participants infected with SARS-CoV-2 was followed, regardless of vaccination status or previous COVID-19 infection (**Table 1**). A female predominance was observed, accounting for 63.89% of cases, with a sex ratio of 0.56. The median age was 39 years, ranging from 23 to 62 years. The infected healthcare personnel were predominantly nurses (30.55%), followed by physicians (27.78%) and nursing assistants (16.67%) (**Table 1**). Most participants worked in occupations with an intermediate risk of exposure (47.22%), followed by high-risk occupations (36.11%). Other general characteristics are summarized in **Table 1**.

Clinical and Biological Background

More than 83% (83.33%) of participants had a history of COVID-19 vaccination, with 66.66% having received two doses and 16.67% one dose (**Table 1**). In

Table 1. Characteristics of the study population.

	Number (n)	Frequency (%)
Number of participants	36	100
Sex		
Male	13	36.11
Female	23	63.89
Sex ratio	0.56	
Age		
Median age	39	
Range	23-62	
Services		
Emergencies	18	50
Hospitalisations	7	19.44
Consultations	5	13.89
Laboratoire	4	11.11
Administration	2	5.56
Profession		
Nurses	11	30.55
Physicians	10	27.78
Healthcare assistants	6	16.67
Other	9	25
Level of risk		
Low	6	16.67
Intermediate	17	47.22
High	13	36.11
Comorbidities		
Asthma and atopy	9	25
Hypertension	5	13.89
Diabetes	2	5.56
No comorbidity	20	55.55
Body mass index		
<18.5 (leanness)	00	00
18.5 - 25 (Normal)	19	58.78
25 - 30 (Overweight)	11	30.55
30 - 40 (Moderate obesity)	6	16.67

Continued

>40 (Severe obesity)	00	(00
History of infection		
No	22	61.11
Yes	14	38.89
1 infection	12	33.33
2 infections	2	5.56
Symptomatic	19	52.78
Asymptomatic	17	47.22
Average time to sampling (extremes)	12.21 months (2 - 24)	
Vaccination		
No	06	16.67
Yes	30	83.33
Number of doses		
0 dose	00	00
1 dose	06	16.67
2 doses	24	66.66
Average time to sampling (extremes)	8 months (3 - 26)	
Vaccines done		
Astra-Zeneca	10	33.33
Johnson & Johnson	2	6.67
Pfizer	17	56.67
ATZ/PFZV	1	3,33
COVID-19 infection		
Simple form	17	47.22
Mild form	19	57.7
Severe form	00	00

addition, 38.89% had a history of COVID-19 infection, including 33.33% with one previous infection and 5.56% with two. None of the participants developed severe forms of the disease, and more than half (52.78%) were asymptomatic (**Table 1**). Other medical histories were dominated by atopy and asthma (25% each), hypertension (13.89%), and diabetes (5.56%) (**Table 1**).

Clinical Course of COVID-19 Cases

During follow-up, no severe cases of COVID-19 were observed. All participants developed either a mild (57.78%) or a simple (47.22%) form of the disease (**Table 1**).

Evolution of IgG Levels According to the Type of Immunization

A progressive increase in IgG levels was observed, with a statistically significant difference ($p < 0.0001$, 95% CI = −187.8 - −63.21), particularly between baseline and the end of follow-up as shown in Figure 1(a). However, comparison between vaccinated and unvaccinated subjects revealed no significant difference

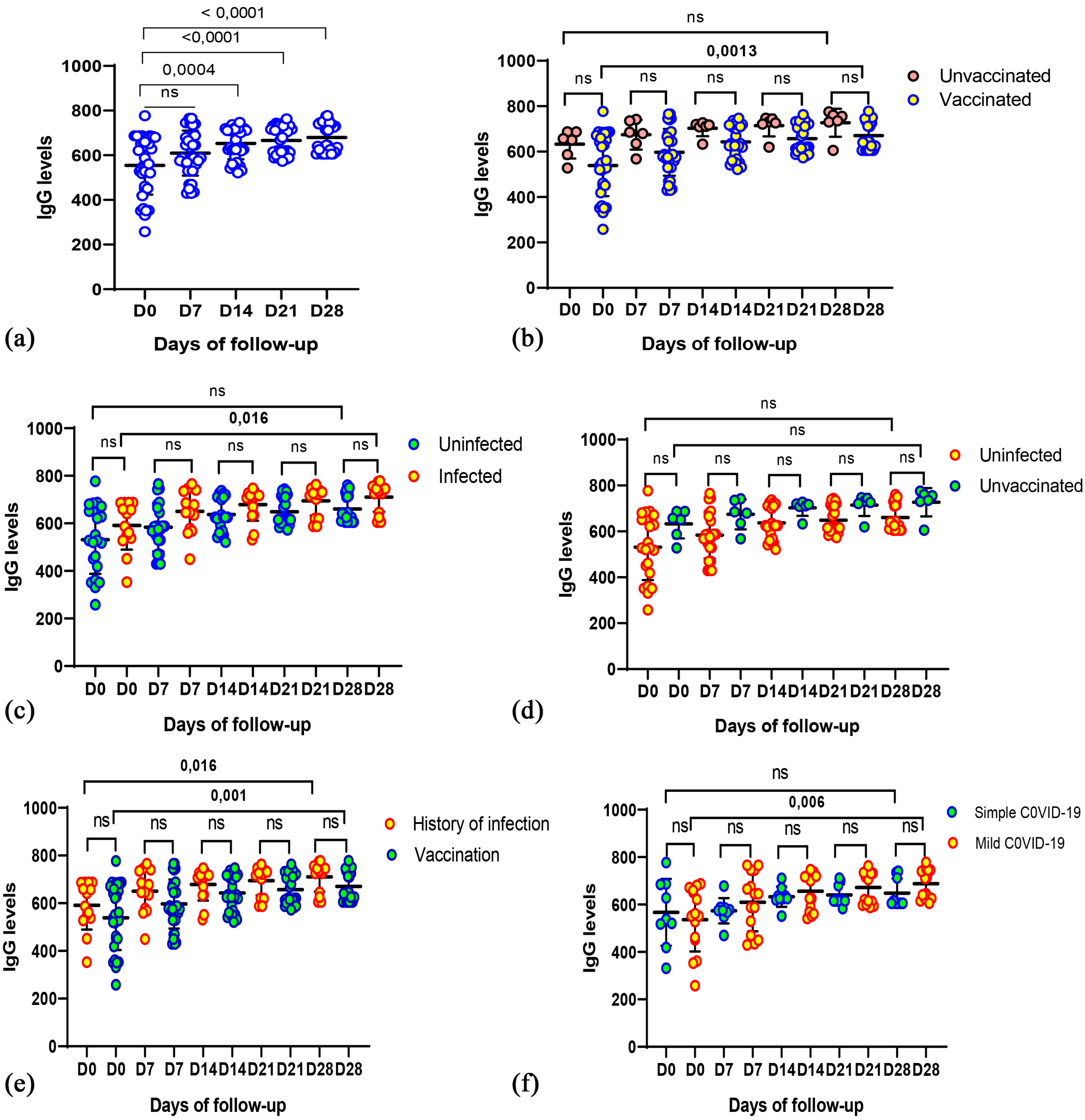

Figure 1. Comparison of IgG average levels. (a) Comparison of IgG average levels at different sampling dates during follow-up; (b) Comparison of IgG average levels between vaccinated and unvaccinated subjects; (c) Comparison of IgG average levels between subjects with and without a history of infection; (d) Comparison of IgG average levels between subjects with no history of infection and no history of vaccination; (e) Comparison of IgG average levels between subjects with a history of infection and vaccinated subjects; (f) Comparison of IgG average levels between different forms of COVID-19.

(**Figure 1(b)**), although a significant increase (p = 0.0013, 95% CI = 37.03 - 204.1) was noted among vaccinated participants between baseline and the end of follow-up. Similarly, there was no difference between participants with and without a previous infection. However, within the previously infected group, a significant difference was observed between baseline and final measurements (p = 0.016, 95% CI = 2.219 - 236.8), as shown in **Figure 1(c)**). These findings suggest that prior immunization promotes enhanced IgG production. This observation was further supported by the absence of significant differences between participants without prior infection and unvaccinated individuals (**Figure 1(d)**), and between previously infected and vaccinated participants (**Figure 1(e)**). When comparing IgG levels across clinical forms of COVID-19, no significant difference was noted between mild and simple cases as shown in **Figure 1(f)**. However,, a significant increase between baseline and final measurements was observed in mild cases (**Figure 1(f)**, p = 0.006, 95% CI = 9.821 - 293.6), suggesting increased IgG production with greater disease severity.

Evolution of IgG Levels According to the Number of Previous Immunizations

The analysis of IgG kinetics based on the number of prior is shown in **Figure 2**. It revealed that, residual titers were relatively higher in previously infected subjects than in vaccinated ones. This increase was more pronounced and progressive in those with a single prior infection. Conversely, in participants with two previous infections, titers rose for approximately 14 days before gradually declining. Among vaccinated participants, residual titers were lower, particularly in those who had received only one dose. However, following infection, IgG levels among those with a single vaccine dose increased rapidly to a peak (around day 14) before declining, while fully vaccinated participants exhibited a more gradual and sustained increase (**Figure 2(a)**). Regardless of the type of prior immunization, IgG production increased following new infection, though titers were initially higher in subjects with no immunization, post-infectious (natural) immunity, or hybrid immunity (infection plus vaccination). By contrast, titers were lower in those with purely vaccine-induced (artificial) immunity (**Figure 2(b)**). Overall, reinfection induced a stronger IgG response in participants with natural or hybrid immunity.

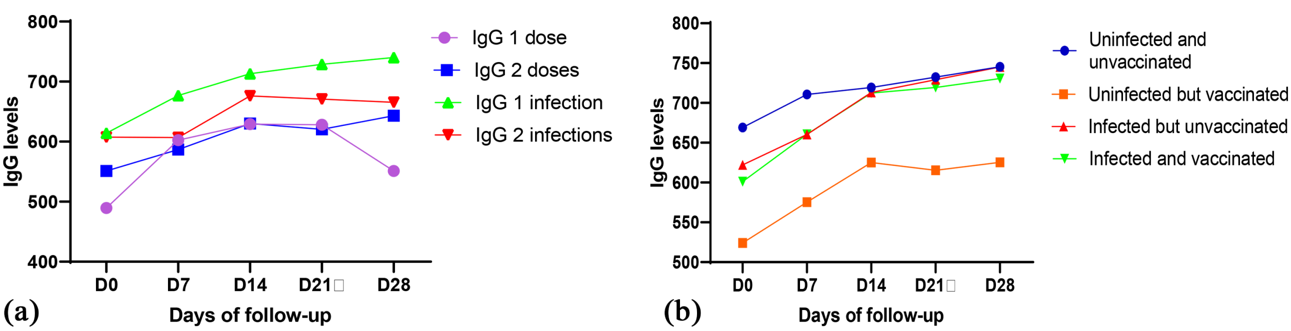

Figure 2. Evolution of IgG average levels according to history of infection and vaccination. (a) Evolution of the IgG average levels according to the number of vaccine doses and history of infections; (b) Evolution of the IgG average levels according to types of immunization.

Evolution of nAb Levels According to the Type of Immunization

Unlike the changes seen in IgG titers, nAb levels did not vary significantly over time. This stability across all follow-up assessments is shown in Figure 3(a)). Comparison between vaccinated and unvaccinated participants showed no

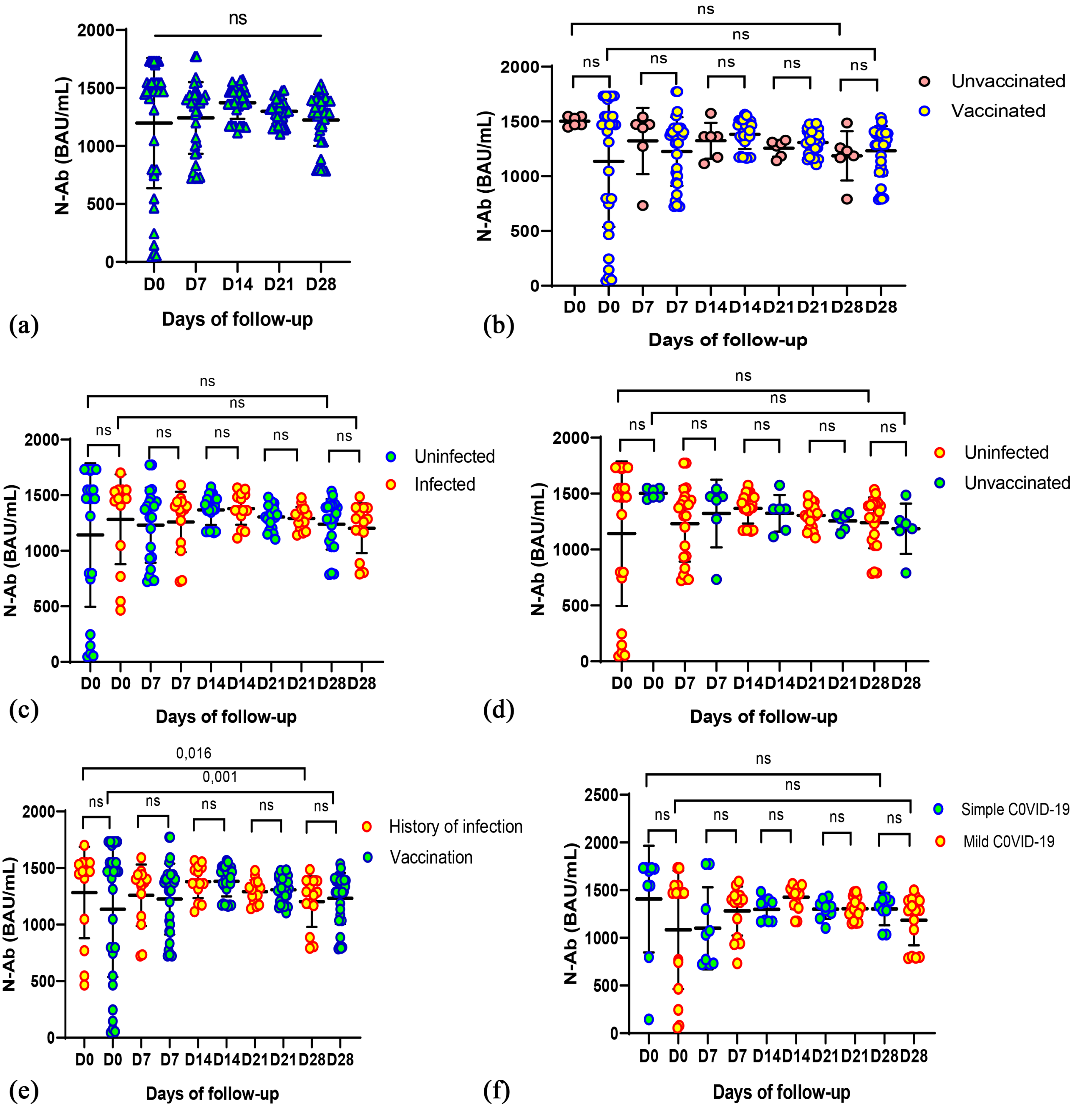

Figure 3. Comparison of neutralizing antibody average levels (nAb). (a) Comparison of nAb average levels at different sampling dates during follow-up; (b) Comparison of nAb average levels between vaccinated and unvaccinated subjects; (c) Comparison of nAb average levels between subjects with and without a history of infection; (d) Comparison of nAb average levels between subjects with no history of infection and no history of vaccination; (e) Comparison of nAb average levels between subjects with a history of infection and vaccinated subjects; (f) Comparison of nAb average levels between different forms of COVID-19.

difference (Figure 3(b)). Similar results were observed between those with and without prior infection (Figure 3(c)), between non-infected and unvaccinated subjects (Figure 3(d)), and between previously infected and vaccinated individuals (Figure 3(e)). However, significant differences were observed between baseline and end-of-follow-up titers in both previously infected (p = 0.016, 95% CI = −230.0 - −9.020) and vaccinated (p = 0.001, 95% CI = −408.0 - −85.13) groups, as illustrated in Figure 3(e), suggesting that infection in pre-immunized individuals enhances nAb production. No difference in nAb levels was found between mild and simple forms of COVID-19 throughout follow-up as shown in Figure 3(f).

Evolution of nAb levels according to the number of previous immunizations

The overall trend in nAb titers indicated an initial decline followed by an increase and then a slower regression. Residual titers were relatively higher in participants with one prior infection or complete vaccination. Upon reinfection, titers tended to decline after day 14. Participants with two previous infections displayed relatively high residual titers that stabilized and then increased after day 14. By contrast, those who had received only one vaccine dose showed very low baseline titers but exhibited a sharp increase peaking on day 14, followed by a gradual decline (Figure 4(a)). This suggests that infection in individuals with a single vaccine dose may elicit stronger nAb production compared to those fully vaccinated or previously infected. Regardless of the type of prior immunization, residual nAb titers followed similar regression patterns, generally beginning after day 14. This decrease was more pronounced among unvaccinated and infection-naïve individuals. Participants with hybrid or vaccine-only immunity exhibited an initial decline during the first week, followed by a rise in the second week and a regression from day 14 onwards. In those with infection-only immunity, a marked decrease was observed until day 14, followed by stabilization (Figure 4(b)).

Comparative Evolutionary Profile of IgG and nAb Levels

Overall, a general trend of increasing IgG levels was observed throughout the follow-up period, contrasted by a decline in nAb levels as shown in Figure 5(a). Similar dynamics were observed when stratifying by infection history (Figure 5(b)) and vaccination history (Figure 5(c)). Thus, regardless of the immunization

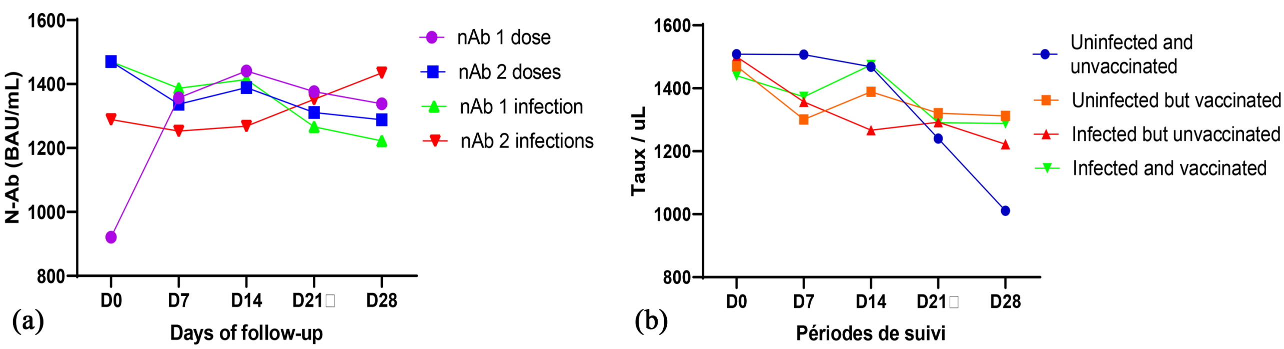

Figure 4. Evolution of nAb average levels according to history of infection and vaccination. (a) Evolution of the nAb average levels according to the number of vaccine doses and history of infections (b) Evolution of the nAb average levels according to types of immunization.

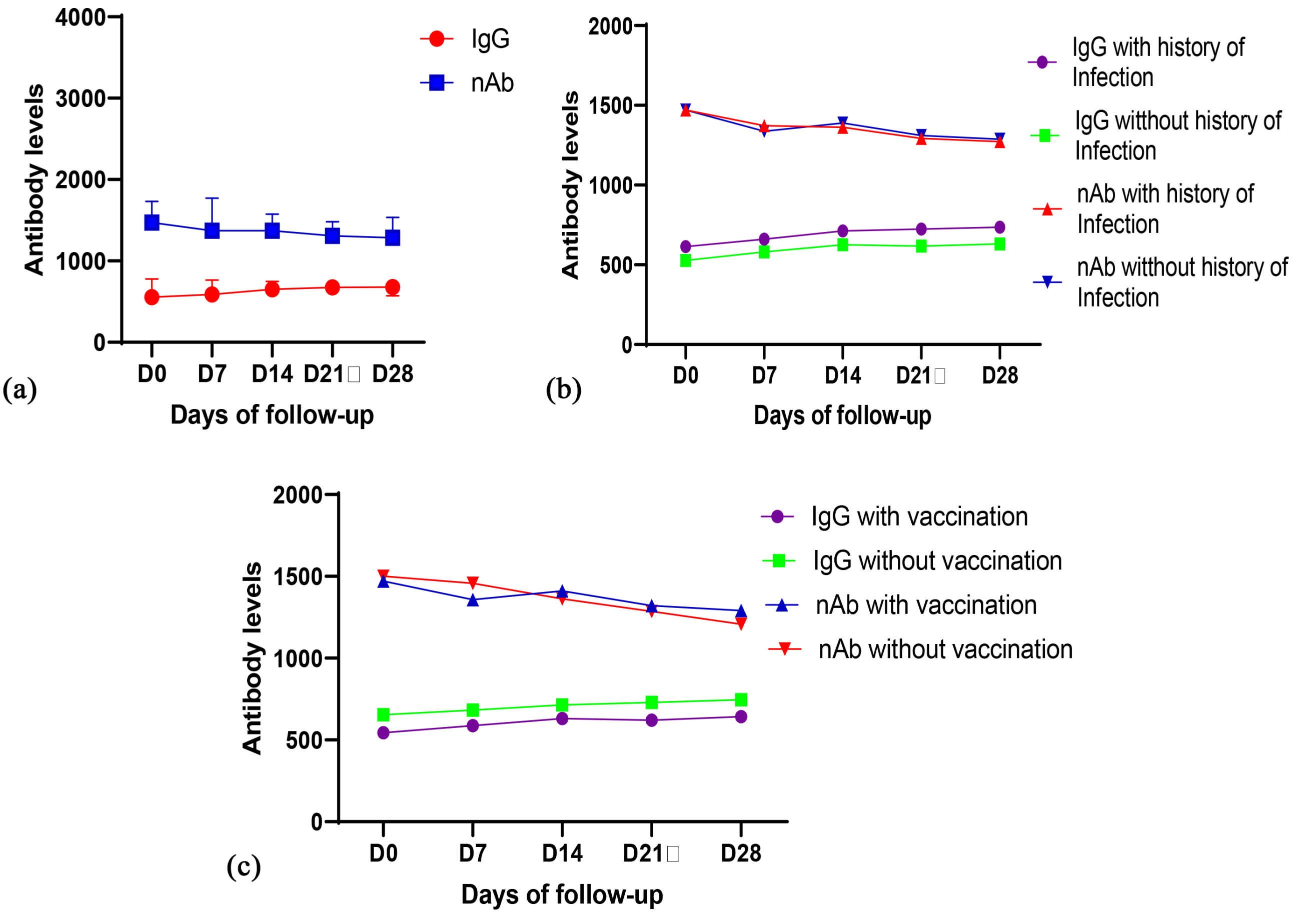

Figure 5. Comparative evolutionary profile of IgG and neutralizing antibody levels. (a) Trend profile of IgG and neutralizing antibody average levels; (b) Evolution of IgG and neutralizing antibody average levels according to history of infection; (c) Evolution of IgG and neutralizing antibody average levels according to history of vaccination.

pathway, both IgG and nAb followed comparable kinetic profiles, consistent with the general pattern.

4. Discussion

Sociodemographic Characteristics of the Study Population

The female predominance observed in our study population is consistent with reports from the literature. According to the World Health Organization (WHO), women accounted for approximately 70% of the global healthcare workforce in 2019 [10]. Similarly, a 2022 study from Canada showed that 75% of healthcare personnel were women [11]. Women therefore constitute a significant proportion of the healthcare sector worldwide. Participants were mostly young adults, with a median age of 39 years, similar to findings by Guiegui *et al.* (2022) in Abidjan, who reported a mean age of 36.7 years among healthcare workers [12]. This observation likely reflects the youthful structure of the Ivorian population. Participants mainly occupied positions with intermediate occupational risk, and most were from emergency (50%), inpatient (19.44%), and outpatient (13.89%) departments. Nurses (30.55%), physicians (27.78%), and nursing assistants (16.67%)

were the most represented categories among frontline workers directly exposed to patients (**Table 1**). These results agree with those of Maddalena Cordioli *et al.* (2022), who also observed a predominance of physicians (29.3%) and nurses (53.1%) [13].

Clinical and Biological Background and Disease Evolution

The absence of severe COVID-19 forms among participants during follow-up could partly be attributed to the high proportion of individuals with prior immunization. Approximately 39% of participants had a history of natural infection, while around 83% were vaccinated (**Table 1**). This strong acquired immunity (both natural and vaccine-induced) may have contributed to preventing progression to severe disease. This observation also supports the hypothesis that the immune systems of African populations may be better adapted to infectious challenges. Indeed, the tropical climate, which promotes frequent exposure to pathogens, could modulate immune responses to SARS-CoV-2 [14].

Influence of Previous Immunizations on IgG Levels

The significant difference ($p < 0.0001$) between IgG titers at diagnosis and at the end of follow-up (**Figure 1(a)**) reflects immune reactivation during infection, consistent with the results by Assaid N. *et al.* [15]. This trend was observed among both vaccinated ($p = 0.001$) and previously infected ($p = 0.016$) participants (**Figure 1(b)** and **Figure 1(c)**). However, comparisons between vaccinated and unvaccinated participants, as well as between previously infected and infection-naïve individuals, revealed no significant differences. This suggests that IgG production was influenced by immunization history but masked by the high overall immunity within the cohort. Given the pandemic context, even unvaccinated or infection-naïve individuals may have encountered SARS-CoV-2 without developing symptoms. Indeed, several studies have shown that asymptomatic patients can develop anti-SARS-CoV-2 humoral responses [16] [17]. Residual IgG titers can persist beyond two years in recovered individuals [7] [8]. In this study, the average time between vaccination and sampling was 8 months, and between infection and sampling was 12.21 months, suggesting that reinfection acts as an immune booster. Despite high immunization, reinfections occurred, consistent with global observations [3] [4]. While IgG levels did not differ between mild and simple forms, titers increased significantly between diagnosis and the end of follow-up among mild cases ($p = 0.006$), supporting the association between symptom severity and antibody production [18] [19]. The higher IgG titers observed are likely due to a higher viral load, which leads to a longer presence of viral antigens and greater inflammation in mild forms. This helps to drive germinal center activity and improve B cell maturation, resulting in greater antibody production against SARS-CoV-2 compared to shorter antigen exposure [20] [21].

Influence of the Number and Type of Previous Immunizations on IgG Levels

Residual IgG titers were higher among previously infected participants than among vaccinated ones, supporting the hypothesis that infection-induced antibodies may persist longer than vaccine-induced ones [15]. A new infection led to a pronounced IgG increase, especially in individuals with a single prior infection, whereas those with two previous infections showed plateauing levels after day 14 (**Figure 2(a)**). Among vaccinated participants, residual titers were lower in those partially vaccinated compared with those fully vaccinated. Incomplete vaccination produces shorter-lived IgG responses that decline faster [22] [23]. During reinfection, titers rose sharply to a peak around day 14 before declining in partially vaccinated individuals, while fully vaccinated participants exhibited a gradual and sustained increase.

Regardless of immunization type, IgG levels increased following infection (**Figure 2(b)**), with the highest titers observed in post-infectious and hybrid immunity. These results are consistent with previous findings showing that prior infection leads to stronger and more durable antibody responses following vaccination [24] [25]. IgG positivity among participants without an immunization history may reflect early IgG appearance, as some studies have reported IgG preceding IgM [7]. Alternatively, these individuals may have experienced unrecognized asymptomatic infections. Cross-reactive immunity from endemic beta coronaviruses such as HCoV-OC43 may also explain detectable antibody responses in infection-naïve individuals [26] [27].

Influence of Previous Immunizations on nAb Levels

In contrast to IgG titers, no significant changes in nAb levels were observed across follow-up or between immunized and non-immunized groups (**Figure 3**). This suggests that prior immunization did not markedly affect nAb production during reinfection, differing from studies reporting higher nAb titers following vaccination [28] [29]. In the same way, Khoury *et al.* observed that nAb titers induced by vaccination were 20% higher than those observed in convalescent individuals [30]. These discrepancies may reflect the high baseline immunity of our cohort. However, a significant increase in nAb titers was observed between baseline and final measurements among previously infected ($p = 0.016$) and vaccinated ($p = 0.001$) participants (**Figure 3(e)**), indicating that infection on an immunized background enhances the nAb response.

No difference was observed between mild and simple clinical forms, suggesting that neither disease severity nor prior immunization significantly influences nAb kinetics. This contrasts with reports showing a lack of detectable nAbs in some asymptomatic or mild cases [31] [32].

Influence of Number and Type of Previous Immunizations on nAb Levels

nAb levels exhibited a biphasic pattern characterized by an initial decline, followed by a transient rise and a gradual regression. This kinetic pattern is consistent with previously published studies [33]-[35]. The observed decrease could be explained by the short half-life of IgM and IgA antibodies [32] [36]. At diagnosis, residual nAb titers were higher among participants with a single prior infection or complete vaccination (**Figure 4(a)**), suggesting comparable persistence between infection-induced and vaccine-induced immunity. Indeed, the durability of nAb depends on the initial level of nAb titers induced, the prolonged presence of the antigen within the body, and the severity of infection [37]. Consequently, the post-infection antibody titers observed could indicate chronic carriage among healthcare personnel, possibly resulting from exposure to a highly immunogenic circulating viral strain, given their constant contact with potentially infected patients. It could also be related to the severity of previous infections. Two vaccine doses generated higher residual titers than two previous infections, in contrast to the findings of Pradenas E. *et al.*, who reported a more rapid decline in vaccinated individuals [38]. This discrepancy may be attributable to the high proportion of previously infected participants within our cohort. However, the progressive increase in titers among individuals with two previous infections, which contrasts with the gradual decline observed in those who were fully vaccinated, suggests a more pronounced booster effect in the former than in the latter. This observation supports the hypothesis of a more effective booster response when the immune system is re-exposed to the same type of immunizing stimulus. Overall, titers peaked around the 14th day of infection before declining (**Figure 4(a)**), consistent with the observations of Assaid N. *et al.* [15], who found peaks between two weeks and a month, and Barnes T.W. *et al.*, who estimated it at around 20 days [39]. However, other studies have reported peaks occurring around the fourth week [40] [41]. Others, on the other hand, point to the fact that hybrid immunity appears to induce longer-lasting nAb responses [42]. Data available on the kinetics of total antibodies show divergent results. Some authors report slower decline and higher nAb titers in people who have received a booster dose [43], while others limit these benefits to uninfected people [44]. The discrepancies observed across studies could be related to population heterogeneity, variations in test sensitivity, or methodological differences.

Our findings indicate that the presence of high residual nAb titers may explain the absence of severe clinical forms, reinforcing the well-established correlation between neutralizing antibody levels and protection against severe disease [35] [38].

Comparative Evolutionary Profile of IgG and nAb Levels

Overall, IgG levels increased progressively, while neutralizing antibody levels declined (**Figure 5(a)**). This pattern suggests that memory immune responses drive the continuous production of IgG upon reinfection, whereas nAb primarily act to prevent severe forms of the disease. The decline observed after the 14th day corresponds to the convalescent phase. This trend was consistent among participants, regardless of whether their immunity was infection- or vaccine-induced (**Figure 5(b)** and **Figure 5(c)**). These results are in agreement with several studies reporting the persistence of IgG alongside a gradual decrease in neutralizing activity over time following infection [5] [45] [46].

Our study has some limitations. Firstly, the small size of our cohort limits the statistical power of the subgroup analyses and does not allow us to conclude with great confidence that there is no difference in the level of nAbs between the two forms of COVID-19. Secondarily, the follow-up period was short, and there is a possibility of previous asymptomatic infections not being recorded in the group of people with no history of infection.

5 Conclusion

Our data indicate that among immunized individuals, residual IgG levels were higher in those previously infected than in those who were vaccinated. Conversely, for nAb, residual titers were higher in individuals with hybrid immunity and vaccination. Moreover, a history of immunization favored an increase in both IgG and nAb production. However, prior infection promoted stronger IgG responses, whereas hybrid immunity and previous vaccination enhanced the production of nAbs. In addition, greater disease severity was associated with higher IgG titers. During a subsequent infection, higher IgG levels were observed in previously infected individuals compared with vaccinated participants, suggesting that the booster effect is more effective when the same mode of immunization is repeated. Overall, a new infection was associated with a general increase in IgG levels, in contrast with a decline in nAbs. This decrease typically occurred around 14 days after the onset of infection, following the antibody peak. These data should guide health authorities in optimizing vaccination strategies in order to determine the schedule for booster doses.

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Ethics Approval

The procedures in this study were approved by the National Ethics Committee for Life and Health (No. 007-22MSHPCMU/CNESVS-Km) and adhered to the principles of the 1976 Helsinki Declaration and subsequent amendments.

Written informed consent to participate in this study was provided by all participants.

Authors' Contributions

YOR, DSR, and G-KAPV conceived and designed the analysis, researched the data, and wrote the manuscript. YOR and AAH performed the analysis and generated the figures. AAUA, SYJ, MLRC, KHG, MS, and OBD were involved in sample collection, laboratory analysis, and recruitment of subjects. DSR, YOR, NK, and SKL were involved in the clinical design of the study and in receiving referrals of participants from other hospitals. YOR, DSR, and G-KAPV edited the manuscript and were responsible for planning and coordinating the research activity. NK and SKL contributed to the discussion and funding acquisition. All authors contributed to the article and approved the submitted version.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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