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Article

The Distinct Absence of a Post-Boost Spike-IgG Antibody Surge in Ugandan Recipients of the Pfizer-BioNTech Vaccine Has Implications for Vaccination Policies

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Abstract: This study aimed to delineate the longitudinal antibody responses to the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) within the Ugandan subset of the Sub-Saharan African (SSA) demographic, filling a significant gap in global datasets. We enrolled 48 participants, collecting 320 specimens over 12 months after vaccination. A validated enzyme-linked immunosorbent assay (ELISA) was used to quantify SARS-CoV-2-specific IgG, IgM, and IgA concentrations (ng/ml) and optical densities (ODs). Statistical analyses included box plots, diverging bar graphs, and the Wilcoxon test with Bonferroni correction. We showed a robust S-IgG response within 14 days of the primary vaccine dose, consistent with global data. Remarkably, we observed no significant surge in S-IgG levels following the booster, contrasting trends other global populations. The S-IgM response was transient, and predominantly established thresholds, reflecting its typical early emergence and subsequent decline. S-IgA increased initially but declined six months post-vaccination, in line with the temporal dynamics of mucosal immunity. Eleven breakthrough infections occurred; however, all were asymptomatic, indicating a protective effect from the vaccination regardless of the participants' initial S-IgG serostatus. The Pfizer-BioNTech COVID-19 vaccine elicited strong S-IgG responses in the SSA demographic. However, antibody dynamics distinctly differed from global data highlight the significance of region-specific research and the necessity for customized vaccination strategies.

Keywords: Pfizer-BioNTech vaccine; SSA; S-IgG Antibody dynamics; S-IgM; S-IgA; SARS-CoV-2; Breakthrough Infections

Introduction

A global health crisis triggered by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 pandemic, necessitated rapid research and the introduction of vaccines. Among these, the Pfizer-BioNTech COVID-19 vaccine (BNT162b2)

showed significant efficacy in clinical trials, mainly undertaken in Western cohorts. There remains a significant gap in knowledge regarding the vaccine's effectiveness in Africa, particularly within Sub-Saharan Africa. Given the unique genetic diversity, endemic diseases, and specific microenvironmental conditions present in Sub-Saharan Africa (SSA), examining the long-term efficacy of vaccines in this region is pivotal. These distinct factors have been substantiated to impact responses to various viral vaccines, highlighting the critical need to understand vaccines' sustained performance and implications within this specific context [1–5]. This study bridges this knowledge gap, examining the longitudinal serological response to the Pfizer-BioNTech vaccine within Sub-Saharan Africa and underscoring potential disparities across diverse populations [6]. To address the pressing need for region-specific data from SSA, we conducted a 12-month analysis exploring the antibody responses to the Pfizer-BioNTech vaccine within a Ugandan cohort. This study is critical in formulating vaccination strategies and discerning the trajectories of long-term immunity in the region. By examining the correlations between baseline antibody levels, breakthrough infections, and subsequent antibody responses, our study aimed to offer essential insights for developing public health strategies appropriately tailored to meet the unique challenges and contexts of the region.

Our study provides a comprehensive analysis of the one-year SARS-CoV-2-specific antibody dynamics (IgG, IgM, IgA) in a region typically underrepresented in global vaccine research, illuminating seroconversion patterns and the influence of baseline serostatus on vaccine effectiveness, with broader implications for booster strategies and breakthrough infections. This research contributes pivotal insights capable of informing and refining vaccination strategies and public health policies throughout Africa by bridging a significant knowledge gap. The findings emphasize the importance of understanding diverse vaccine responses to facilitate the formulation of customized and pragmatic immunization strategies.

Materials and Methods

Study population and study design

In this study, we collected 320 specimens from a cohort of 48 individuals who received two doses of the PFZ vaccine on day 0 and day 30. Participants were monitored for 12 months after their initial vaccination, with samples collected from March 21, 2021, to January 6, 2023. Of the 48 participants, 45.8% (n=22) were female and 54.2% (n=26) were male. The age ranged from 19 to 49 years, with a median of 30 years and an Interquartile Range (IQR) of 25–35.3 years. Blood samples were collected prior to the administration of both the first and second doses of the Pfizer-BioNTech COVID-19 Vaccine, BNT162b2. In addition, samples were collected on Days 14 and 28 following the initial dose. Approximately 30 days following the initial vaccination, a booster was administered, with samples subsequently collected on Days 14 and 28 and then at six, nine and twelve months after the first dose, as shown in Figure 1.

	Priming Dose	Booster Dose						
								
n = 48	D0	D14PP	D28PP	D14PB	D28PB	M6PP	M9PP	M12PP

Figure 1. The Pfizer BioNTech Vaccination and Sample Collection schedule.

Binding antibody ELISA to detect SARS-CoV-2-specific IgG, IgM, and IgA levels.

We used a validated enzyme-linked immunosorbent assay (ELISA) to quantify the presence and levels of specific SARS-CoV-2 antibodies, targeting both spike and nucleoprotein antigens in the specimens, quantifying IgG, IgM, and IgA concentrations in ng/ml through detected optical densities at 450 nm. The established cut-off values for antibody positivity within this population were: S-directed IgG (0.432), IgM (0.459), and IgA (0.226); and N-directed IgG (0.454), IgM (0.229), and IgA (0.225). Further details on the ELISA protocol and cut-off criteria can be found in our previous publication [7].

Statistical methods

We used box plots to visually represent medians, means, and quartiles for our statistical analysis. Diverging bar graphs were used to show the percentage of seroconversion at each follow-up time point. We applied the Wilcoxon test for pairwise comparisons to determine significant differences in antibody responses across time points, with a Bonferroni correction to adjust for multiple testing. Given the missing data/samples across time points, we opted for unpaired tests. A threshold of $p > 0.05$ was deemed non-significant (ns). Significance levels were as follows: * for $p \leq 0.05$, ** for $p < 0.01$, *** for $p < 0.001$, and **** for $p < 0.0001$.

Results

Post-vaccination Trends Showed a Robust S-IgG Response, with No significant Booster Dose Effect, Sub-optimal S-IgM, and Time-Limited S-IgA Elevation

We first examined the temporal dynamics of antibodies targeting the Spike protein, starting with the baseline S-IgG antibody responses at Day 0 (D0) and then examining their median values at subsequent time points. Of the 48 participants in the study, 43 had available baseline S-IgG data. These individuals were stratified based on their S-IgG seropositivity at baseline: those with levels at or above the S-IgG cutoff were designated as S-IgG+ (shown in red), while those below the threshold were labelled as S-IgG- (represented in blue), as illustrated in Figure 2. A marked rise in S-IgG antibody responses from day 0 (D0) to 14 days post-priming dose was evident for both S-IgG positive (S-IgG+) and negative (S-IgG-) groups, with the increase being more pronounced for the S-IgG- group (Figure 2A and 2B). Notably, while the initial immune response at D0 differed significantly between the two groups, with S-IgG+ participants displaying higher responses, the post-vaccination S-IgG antibody distributions became indistinguishable at subsequent intervals.

After 14 days post-priming, the concentrations of S-IgG antibodies remained relatively comparable between both groups. Notably, there was no discernible enhancement in immune responses after the booster dose administration.

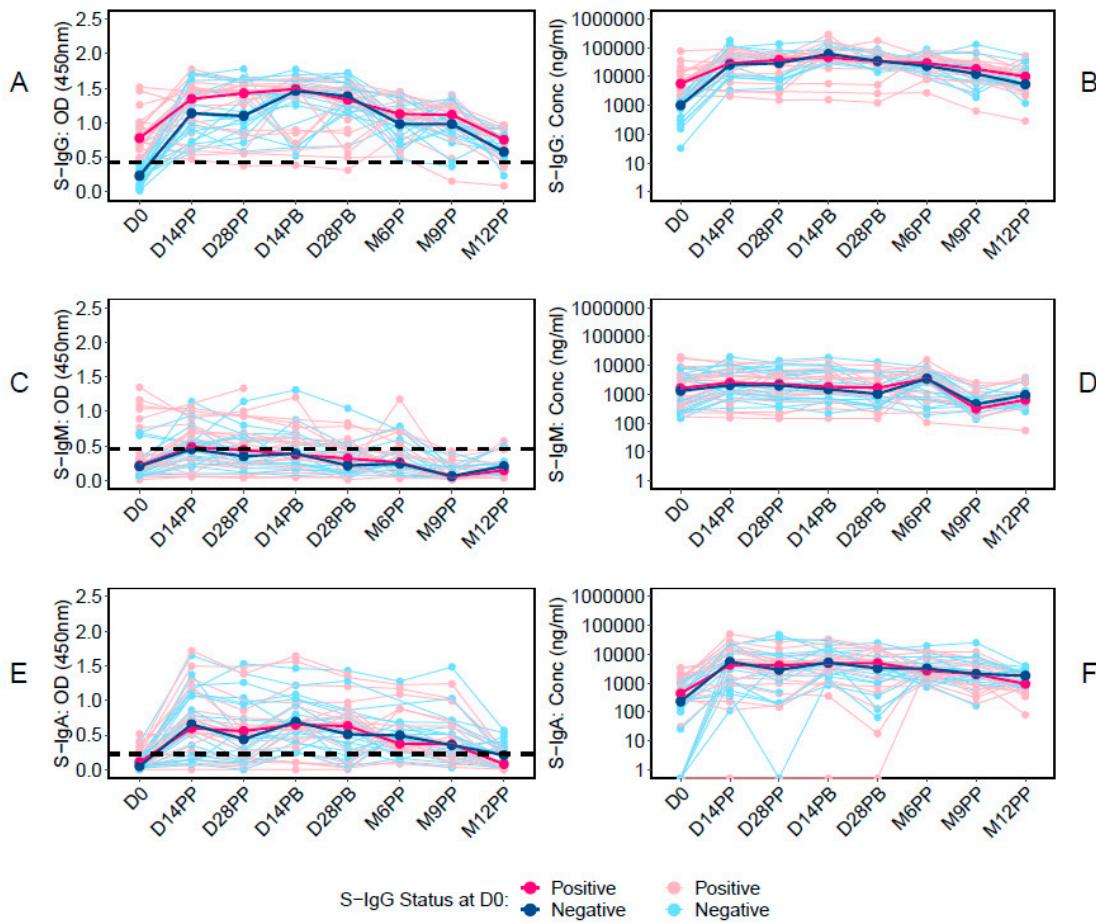


Figure 2. Individual profile graphs categorised by baseline S-IgG seropositivity.

On the other hand, S-IgM antibody responses remained low throughout, with most participants registering responses below the cutoff. No distinction was observed in S-IgM antibody levels between S-IgG+ and S-IgG- participants at any point, as depicted in Figures 2C and 2D. In contrast, S-IgA antibodies surged exponentially within the first 14 days post-priming. This trend persisted until the sixth month post-priming before a noticeable decline, as shown in Figures 2E and 2F. Notably, there were no significant variations in S-IgA responses between S-IgG+ and S-IgG- participants at any given time, suggesting equivalent S-IgA immune responses across the timeframes evaluated.

These data highlight a robust S-IgG response post-vaccination, a suboptimal S-IgM response, and a consistent S-IgA response that eventually declines after six months. The findings offer valuable insights into the antibody profile following vaccination and supports the importance of monitoring these responses over time.

Rapid and Sustained Seroconversion of S-IgG and S-IgA Following Primary Vaccination, but Transient S-IgM Seropositivity

Using predefined cutoffs of 0.432 for S-IgG, 0.459 for S-IgM, and 0.226 for S-IgA [7], participants were categorised based on their S-IgG positivity as positive or negative at the initial time point. This classification provided the count (and percentages) of participants exhibiting positive or negative results for any antibodies at the respective time points. All 320 samples contributed to this classification, with the sample distribution for each time point depicted in Figure 1. At the beginning of the study (Day 0), 47% of the participants were without S-IgG antibodies. By Day 14 post-primary vaccination, all participants exhibited S-IgG positivity, which remained above 80% for the study duration, Figure 3A. Initially (Day 0), 21% of the participants demonstrated the presence of S-IgM antibodies, which increased to 53% by D14PP. Nevertheless, as depicted in Figure 3B, most participants experienced a decline in antibody responses after reaching a peak, dropping to 27% six months post-primary dose, and showing a total absence of S-IgM seropositivity nine months after the primary vaccination. The percentage of S-IgA-positive participants rose from 21% on Day 0 to 71% fourteen days post-prime, as illustrated in Figure 3C. This upward trend persisted until six months post-primary vaccination, at which point it began to decline, eventually stabilising at 41% by 12 months post-primary vaccination.

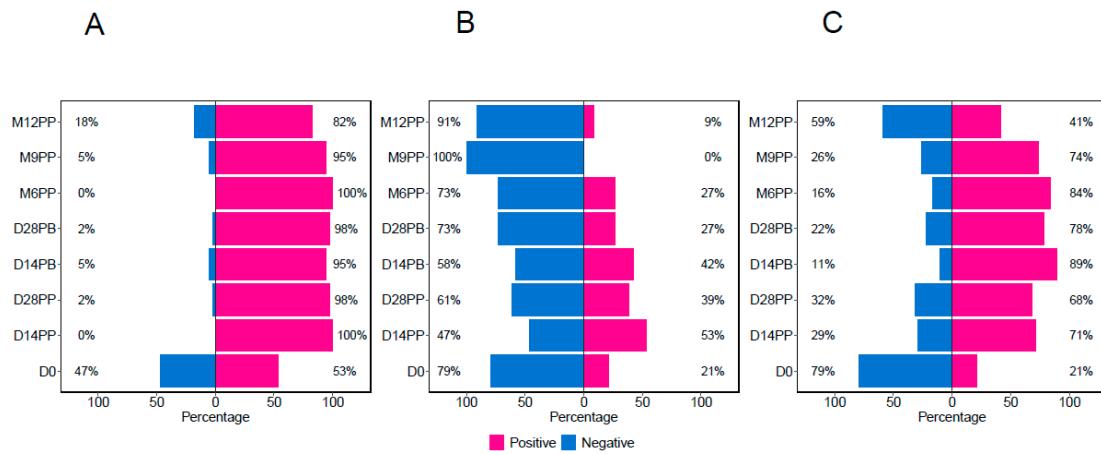


Figure 3. Frequencies of Spike-directed seroconversion.

The use of box plots and an unpaired Wilcoxon test highlighted significant dynamics in antibody responses to the S-antigen over time. Specifically, we observed a marked increase in S-IgG antibody OD values and concentrations from day 0 to day 14 post-prime, with high levels persisting until day 28 post-boost. On day 0, the OD values were 0.464 (IQR 0.250, 0.793), and concentrations were 40.986 BAU/ml (IQR 20.314, 113.864). By day 14 post-prime, these had increased to 1.247 (IQR 0.850, 1.474) and 534.576 BAU/ml (IQR 204.062, 1257.831). Elevated levels persisted until day 28 post-boost, with OD values at 1.330 (IQR 1.147, 1.489) and concentrations at 642.461 BAU/ml (IQR 341.770, 993.056). However, a notable decline in S-IgG OD levels was evident from six months post-prime to twelve months post-prime, summarised in Table 1. Notably, the decline in S-IgG antibody concentrations was not statistically significant, as they remained stable throughout the follow-up period, Figures 4A and 4B. In contrast, we observed relatively modest S-IgM antibody responses, which substantially reduced after six months post-priming (Figures 4C and 4D). Concurrently, a significant increase in S-IgA antibody levels was observed on day 14 following the initial dose, and these elevated S-IgA levels persisted until month nine post-prime, where a significant decline in S-IgA OD responses was evident (Figures 4E and 4F). These findings offer valuable insights into the temporal dynamics of the Pfizer vaccine-induced antibody

responses against the S-antigen, shedding light on potential correlates of immunity and providing guidance for future vaccination strategies.

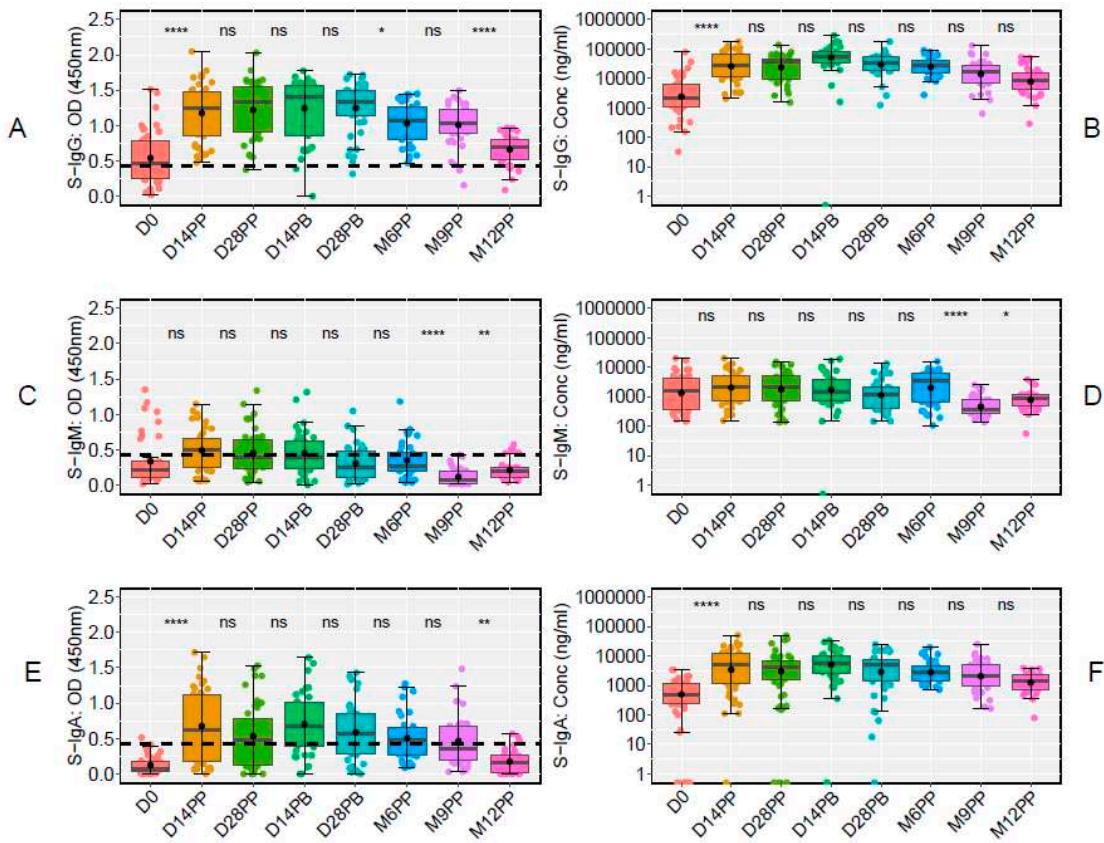


Figure 4. Comparing Spike-directed antibody responses using boxplots.

Post-Vaccination Longitudinal Analysis Unveiled Breakthrough Infections with no Significant Difference by Baseline S-IgG Serostatus

Through a pairwise analysis of antibody OD levels (Figure 5A) and concentrations (Figure 5B), we constructed heatmaps to represent the median fold changes in Spike antibody responses between consecutive time points. Increased responses were visually highlighted in red, while reduced responses were indicated in green. The data indicates pronounced fold increases in S-IgG and S-IgA antibody responses compared to D0, although changes between adjacent time points remained marginal. Additionally, subtle variations in S-IgM between pairwise time points were noted.

A distinct rise in N-IgG antibody levels after a completed vaccination regimen was indicative of an infection. Participants manifesting this surge, 14 days following their complete vaccine dosage, were classified as breakthrough cases. An 11-fold escalation in N-IgG levels signified a confirmed infection. Six months after full vaccination, a noticeable rise in infected participants was observed. In total, 11 individuals were identified as breakthrough: seven became infected six months post vaccination, two at nine months, and two at a year post prime. When stratified by baseline S-IgG status, five participants were previously S-IgG positive, five were S-IgG negative, and one remained unclassified due to the absence of initial S-IgG data, Figure 5C.

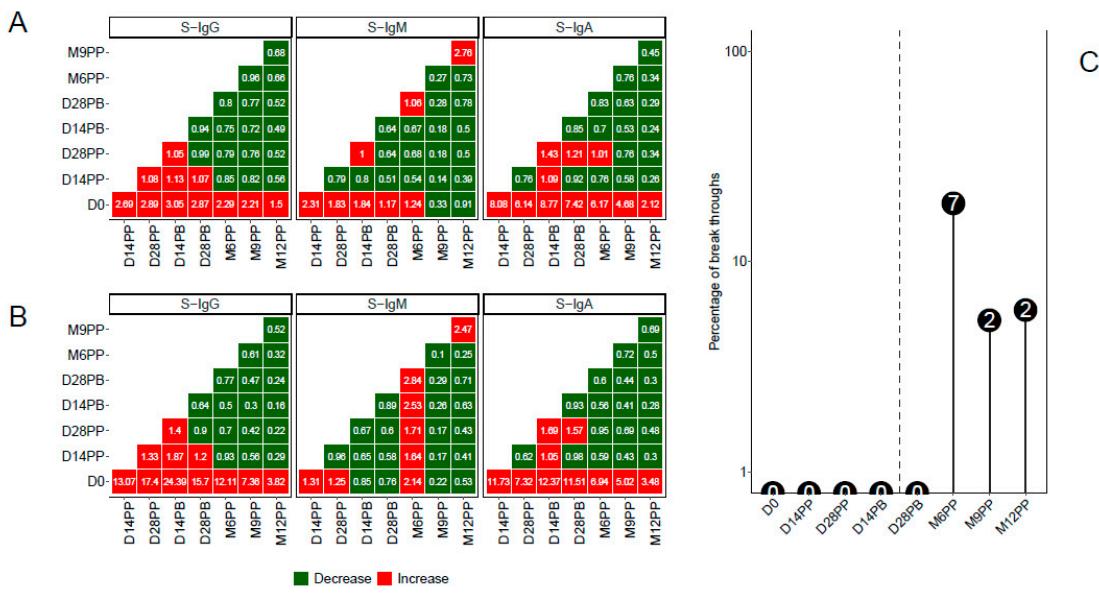


Figure 5. Fold changes in Spike-directed Antibody Levels and Frequency of Breakthrough Infections Post-Vaccination.

The Early Rise in S-IgG Antibody Responses in Seronegative Participants Subsequently Aligned with Seropositive Counterparts Throughout the Subsequent Study Duration

At the study's onset (D0), of the 48 participants, 23 tested positive for S-IgG, 20 tested negative, and five lacked baseline specimens. Notably, there was a significant decline in S-IgG OD antibody responses at 12 months post-prime relative to 9 months, as illustrated in Figures 6A and 6B. Modest levels of S-IgM were observed in these participants (Figures 6C and 6D), with a marked rise in S-IgA antibodies from D0 to D14PP, persisting until M9PP before a significant decline (Figures 6E and 6F).

Among the 20 participants initially lacking S-IgG antibodies, we observed a significant increase in S-IgG antibodies from the day of vaccination to two weeks post-vaccination, sustained until a month after the booster, with a notable decline in OD levels by the sixth month, but consistent antibody concentrations across all study time points without any significant rise post-boost, as shown in Figures 7A and 7B. Participants with a baseline seronegative status showed reduced S-IgM antibody levels (Figures 7C and 7D). However, S-IgA responses rose from D0 to D14 after the initial vaccination and stabilized (Figures 7E and 7F). In our findings, baseline seronegative participants showed a comparable IgG antibody trajectory to their seropositive counterparts, except that the latter group did not exhibit a post-prime boost in antibody concentrations. This pattern did not change when breakthrough participants were excluded from the analysis, Supplementary Figure 3.

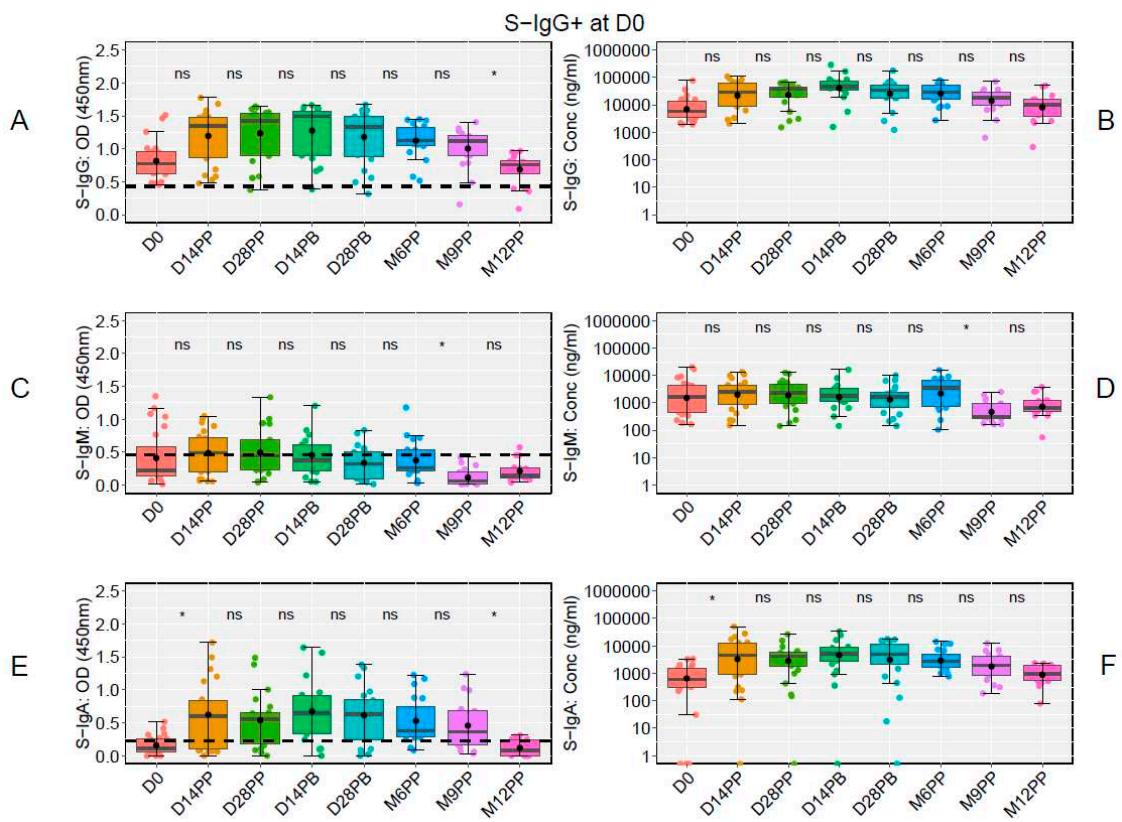


Figure 6. Boxplots comparing Spike-directed Antibody Responses Among Individuals with Baseline S-IgG Antibodies.

Limited Early Presence of N-Directed Antibody Responses but Significant Increase by 12 Months Post-Prime in Pfizer-BioNTech COVID-19-Vaccinated Individuals

Within the N-directed antibody response context, participants, irrespective of their baseline S-IgG status, exhibited low N-directed IgG responses, illustrated in Supplementary Figures 1A and 1B. Initially, only a minimal proportion were N-IgG seropositive at baseline; however, this markedly increased to 62% at 12 months post-prime (M12PP), as depicted in Supplementary Figure 1C. Moreover, the presence of low levels of N-IgM was a consistent observation among both S-IgG+ and S-IgG- participants, as demonstrated in Figures 1D and 1E. The percentage of participants testing positive for S-IgM decreased from 51% at baseline to 24% on Day 28 post-boost (D28PB) before experiencing a rise to 57% six months following the initial dose (Supplementary Figure 1F). This rise could be attributed to subsequent breakthrough infections. We consistently observed low levels of N-directed N-IgG and N-IgM antibodies throughout the study, as depicted in Supplementary Figures 2A-2D. The analysis revealed no statistically significant variations in these levels over time.

Discussion

In the global response to the SARS-CoV-2 pandemic, the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) played a pivotal role, demonstrating notable efficacy in diverse populations worldwide. However, until now, there is a striking lack of data regarding its performance within the African demographic, particularly SSA. This gap is particularly significant considering the

distinct and extensive genetic diversity [8–10], environmental, and epidemiological activation microenvironment prevalent within African populations [1,11], that do influence vaccine-induced immune responses [6,12]. Our study provides critical insights into the dynamics of longitudinal antibody responses post-Pfizer-BioNTech COVID-19 vaccination within the SSA demographic, presenting findings that align with and differ from international datasets. The significant and persistent S-IgG response observed within 14 days after the initial dose is consistent with global data, underscoring the vaccine's potential to induce potent immunity across a wide range of demographics [13]. This robust response was sustained throughout, regardless of participants' baseline S-IgG serostatus. While the lack of a pronounced increase in S-IgG levels post-booster in our cohort aligns with some populations [14], it contrasts with many others [15,16], highlighting differential immune dynamics that merit further investigation. Numerous factors might account for these disparities: genetic divergences, unique HLA patterns in the African populace affecting antigen processing [8], protective advantages from earlier SARS-CoV-2 exposure [17], and a consistently low booster response in those with prior exposure, as noted in studies on other viruses [18]. Further research is warranted to elucidate this. The transient and subdued S-IgM response observed post-vaccination, largely falling below established thresholds, reflects its customary early emergence and subsequent decline as memory responses develop. The limited detection of this isotype post-vaccination is consistent with the induction of a mature memory response, as previously observed in natural infections in this population [19] and others [20,21]. S-IgA, vital for mucosal defence against SARS-CoV-2 [22], showed a significant trend: an initial increase followed by a decline six months after the primary vaccination, highlighting the need for ongoing surveillance to ensure lasting protective immunity. Our analysis showed a comparable frequency of breakthrough infections between participants with baseline S-IgG positive and those with baseline S-IgG negative serostatus; the differences were not statistically significant. Regardless of their baseline serostatus, all individuals experiencing breakthrough infections remained asymptomatic, highlighting the potential protective benefits of vaccination [23]. These data also align with the concept of "hybrid immunity," suggesting that a synergistic effect of natural immunity and vaccination might enhance overall protection. In our study, we examined the longitudinal profiles of the Pfizer vaccine within the SSA context, specifically focusing on the Ugandan demographic. While many of our findings mirrored global trends, the unique antibody dynamics we identified underscore the significance of tailored, region-specific research. Such findings reinforce the necessity of understanding regional distinctions to effectively shape and implement vaccination strategies and public health policies in diverse settings.

Several critical implications emerge in our study examining the longitudinal profiles of the Pfizer vaccine in SSA. We observed a robust S-IgG antibody response post-vaccination, consistent with global trends [14,24], underscoring the vaccine's ability to induce potent adaptive immunity in the African cohort. Post-vaccination antibody peaks were higher than those following infection; however, the subsequent trajectory aligned with hybrid immunity, most of the time. The transient nature of the S-IgM response, mirroring findings from other populations, suggests the typical transient nature of these antibodies post-vaccination rather than vaccine inefficacy. Notably, the early surge and subsequent decline of S-IgA antibodies at six months offers insights into the temporal dynamics of mucosal immunity [14,25], which plays a crucial role against respiratory pathogens like SARS-CoV-2 [26,27]. Our analysis of breakthrough infections in participants devoid of symptoms, underscored the potential protectiveness of the elicited immunity [28,29].

Furthermore, the lack of a pronounced surge in S-IgG antibodies post-second dose in our cohort contrasts with other populations [16], hinting at unique genetic or environmental determinants in SSA that might influence the vaccine's response. The limited surge in antibody response after the second dose might indicate a potentially altered prime-boost strategy for the

Ugandan population. Perhaps a longer interval between doses, as shown in mice studies, might yield a different outcome [30]. This difference necessitates deeper evaluation into genetic predispositions, especially considering the HLA diversity in Africans and its potential impact on adaptive vaccine responses.

While this study provides insights into the antibody dynamics post-Pfizer vaccination among the Ugandan subset of the SSA population, it is not without limitations. First, the participant sample size of 48 might only partially capture the diverse and heterogeneous SSA demographic [31–33]. Furthermore, we primarily focused on binding antibody responses, omitting the evaluation of antibody functionality [34]. The significance of T-cell-mediated immunity [35,36], crucial for sustained viral defense, was also not examined in our study. Furthermore, while the 12-month period provides a thorough overview, it may not capture the intricacies of long-term immune memory or potential changes in immunity that arise later. Furthermore, considering the continuous emergence of new SARS-CoV-2 variants, a definitive assessment of the vaccine's performance against these novel strains in this setting is yet to be established. Considering our findings, we recommend comprehensive studies across varied African demographics. Given the unique genetic diversity and environmental and health challenges faced in the African setting, it is crucial to conduct region-specific studies. Such research should focus on understanding the efficacy of booster doses across various age groups and health statuses, especially in individuals with co-existing endemic infections such as malaria or HIV. Moreover, studies should also evaluate the durability of vaccine-induced immunity in the African population, considering local disease prevalence and potential interactions with other prevalent infections. Understanding these factors can offer insights into optimizing vaccination strategies tailored to the African context. There is a need to investigate T-cell responses post-vaccination for a holistic understanding of vaccine-induced immunity. The observed dynamics in both baseline seropositive and seronegative individuals suggest the potential necessity for periodic booster doses. Future studies should also consider the relationship between genetic factors, vaccine response, and breakthrough infections in this population. Evaluating the vaccine in relation to prevalent SARS-CoV-2 strains in SSA and the effects of prior natural infections could guide optimal vaccination strategies.

In conclusion, this study highlighted the antibody responses to the Pfizer-BioNTech COVID-19 vaccine in SSA, a demographic previously underrepresented in global datasets. We observed a strong S-IgG response, with notable differences in S-IgM and S-IgA dynamics and responses relative to baseline S-IgG serostatus. Notably, a post-boost surge was absent, emphasizing the need for customized vaccination plans for areas with unique environmental and genetic profiles, like SSA. Region-centric studies are vital to ensure that vaccination strategies resonate with diverse serological and genetic contexts, enhancing their effectiveness.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author contributions: Conceptualization and methodology: JSer. Laboratory investigation: JSK, JSem, GKO, IS, LK, SM, BG, and the COVID-19 Immunoprofiling team. Data curation, software, and formal statistical analysis: VA and JSer. Writing- original draft; JSer. Writing- reviewing and editing; PK, VA and GKO. Project Supervision: JSer and PK. All authors read and approved the final manuscript.

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Ethics approval and consent to participate: The study received approval from the Uganda Virus Research Institute's Research and Ethics Committee (GC/127/833) and the Uganda National Council for Science and Technology (HS637ES). All procedures adhered to the respective ethical guidelines. Written informed consent was obtained from all participants.

Data availability statement: This study presents all original data generated. Please contact the corresponding author for further inquiries or access to the raw data supporting the article's conclusions. The authors will provide this data without undue reservation.

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Conflict of Interest: The authors confirm that no commercial or financial relationships exist that could lead to a potential conflict of interest.

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