Persistence and Waning of Natural SARS-CoV-2 Antibodies Over 18 Months: Long-Term Durability of IgG Humoral Response in Healthcare Workers

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INTRODUCTION

SARS-CoV-2 infection is highly protective against reinfection and symptomatic disease.[1] However, the duration of natural immunity from prior infection remains largely unknown with very limited data on SARS-CoV-2 antibody persistence beyond 8 months.

We characterized the long-term durability of humoral response in seropositive healthcare workers (HCWs) in a 2-phase study (10 and 18 months). After a 10-month follow-up, 77% of seropositive subjects maintained seropositivity.[2]

METHODS

We conducted this prospective study, monitoring serum IgG anti-SARS-CoV-2 titers among seropositive HCWs after the first COVID-19 pandemic wave in Spain (baseline study: April 2020). In the current research, 134 seropositive HCWs after 10 months were monitored expanding follow-up to 18 months.

Enzyme immunoassay developed by DIA.PRO (https://www.diapro.it/products/covid-19-igg-elisa/) was used to measure serum anti-nucleocapsid and anti-spike protein IgG antibody titers against SARS-CoV-2 (clinical sensitivity: 98–100%; specificity > 98%) throughout the entire study. It is noteworthy that the same assay belonging to the same badge was used to determine antibody titers. This test detects specific subunits of spike and nucleocapsid proteins, and this specificity explains why antibody titers measured in the study are not affected by vaccination (no impact in antibody titers maintaining or waning was observed, with no significant differences in slopes [Mann-Whitney U test, $p = 0.17$] and sero-reversion percentage between vaccinated and unvaccinated [$p = 0.10$]).

The global prevalence of sero-persistence was provided as a pooled probability (95% confidence interval was calculated by bootstrap estimation). Linear mixed models were used to investigate antibody waning. Assuming antibody levels fell exponentially, the natural log-transformed titers were modeled over time. Models were constructed using random intercept (individual) and slope (months since initial titer).

RESULTS

One hundred and thirty-four seropositive subjects (median age: 46.0 years; 68.7% female) completed the 18-month follow-up, with a median (IQR) [range] follow-up of 527 (523–533) [438–560] days (17.56 months) between the baseline (April 2020) and the final measurement (November 2021).

Considering that the prevalence of sero-persistence in the first follow-up period (10 months) was 76.79% (235/306), and the prevalence of sero-persistence was 59.7% (80/134) in the second follow-up period (18 months), the global sero-persistence probability, by bootstrap estimation with $R = 500$, was 45.92% with a 95% confidence interval between 39.03 and 52.45%.

Regarding factors associated with sero-persistence over time, maintaining seropositivity was observed more frequently in the third ($p < 0.001$) and second ($p = 0.001$) tercile of baseline levels of antibody titers (Table 1).

To project the time to loss of antibodies, we used a linear mixed baseline model to extrapolate the mean time to cross the threshold of 1.1A.U. (mean time to loss of antibodies). On average, subjects showed detectable concentrations of IgG anti-SARS-COV-2 up to 471.74 (95% CI: 432.43–511.06) days from baseline (Fig. 1).

DISCUSSION

While symptomatic SARS-CoV-2 infection following COVID-19 vaccination is not an infrequent phenomenon,[3] reinfection after natural infection with SARS-CoV-2 is rare.[1,4] This finding indicates that the immune response induced by natural infection is very effective and longer lasting than that induced by vaccination.[5] It is, therefore, crucial to clearly understand the duration of this effective natural immune response, to optimize the vaccination strategy, especially in HCWs.

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Table 1 Demographic and Clinical Characteristics, by Seroreversion Status, and Univariate and Multivariate Logistic Regression Models for Identification Factors Associated with Seroreversion Status

		Non-seroreversion (n = 80)	Seroreversion (n = 54)	P value	Univariate model	P value	Multivariate model	P value
					OR (95% CI)		OR (95% CI)	
Age (years)	< 45 years	32 (52.0%)	30 (48.0%)	0.076	Ref.	–	Ref.	–
	≥ 45 years	48 (66.7%)	24 (33.3%)		0.53 (0.26–1.07)	0.078	0.71 (0.31–1.64)	0.427
Sex	Female	51 (55.4%)	41 (44.6%)	0.136	Ref.	–	Ref.	–
	Male	29 (69.0%)	13 (31.0%)		0.56 (0.25–1.19)	0.138	0.42 (0.17–1.08)	0.071
Baseline IgG anti-SARS-CoV-2 antibody titer[1]	T1	7 (20.6%)	27 (79.4%)	< 0.001	Ref.	–	Ref.	–
	T2	27 (60%)	18 (40%)		0.18 (0.06–0.48)	0.001	0.16 (0.05–0.46)	0.001
	T3	45 (83.3%)	9 (16.7%)		0.06 (0.02–0.16)	< 0.001	0.06 (0.02–0.18)	<0.001
Exposure risk	Non-high grade	23 (51.1%)	22 (48.9%)	0.149	Ref.	–	Ref.	–
	High grade	57 (64%)	32 (36%)		0.59 (0.28–1.22)	0.151	0.59 (0.25–1.40)	0.235
COVID-19 symptoms	No	25 (52.1%)	23 (47.9%)	0.179	Ref.	–	Ref.	–
	Yes	55 (64%)	31 (36%)		0.61 (0.30–1.26)	0.181	0.65 (0.26–1.59)	0.344
Infection category	Asymptomatic/ mild	66 (58.4%)	47 (41.6%)	0.479	Ref.	–	Ref.	–
	Moderate/severe	14 (66.7%)	7 (33.3%)		0.70 (0.25–1.83)	0.480	1.12 (0.30–4.24)	0.865
Vaccinated	No	7 (87.5%)	1 (12.5%)	0.098	Ref.	–	Ref.	–
	Yes	73 (57.9%)	53 (42.1%)		1.41 (0.64–3.23)	0.400	1.21 (0.45 – 3.27)	0.704

Statistical inference was performed using chi-square test or Fisher test when needed
COVID-19 coronavirus disease 2019, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, IgG immunoglobulin G
[1]*One patient was excluded because a re-infection was documented during the follow-up*

To the best of our knowledge, this is the first report to evaluate the kinetics and durability of SARS-CoV-2 antibodies over a period of 18 months, providing further insight into the nature of post-infection immunity. A significant percentage of subjects, close to 50%, maintained detectable antibody levels 18 months after infection, although with a significant decline in most. Additionally, the model predicts a mean time to loss of antibodies of 471 days (about 16 months) from baseline.

Antibody titers at baseline was the unique significant factor associated with an increased probability of maintaining detectable antibody levels over time, but we must consider that higher antibody levels have been associated with the severity of SARS-CoV-2 infection.

Limitations of the current study include the absence of neutralizing antibodies measurement, although correlation between anti-SARS-CoV-2 antibodies and neutralizing antibodies has been largely described.[6] Additionally, we tested the longevity of antibodies against SARS- CoV-2 variants involved in the first wave of the pandemic and no other later variants, but this issue may be considered marginal to the results since no clinically relevant SARS-CoV-2 reinfection was detected in our follow-up study.

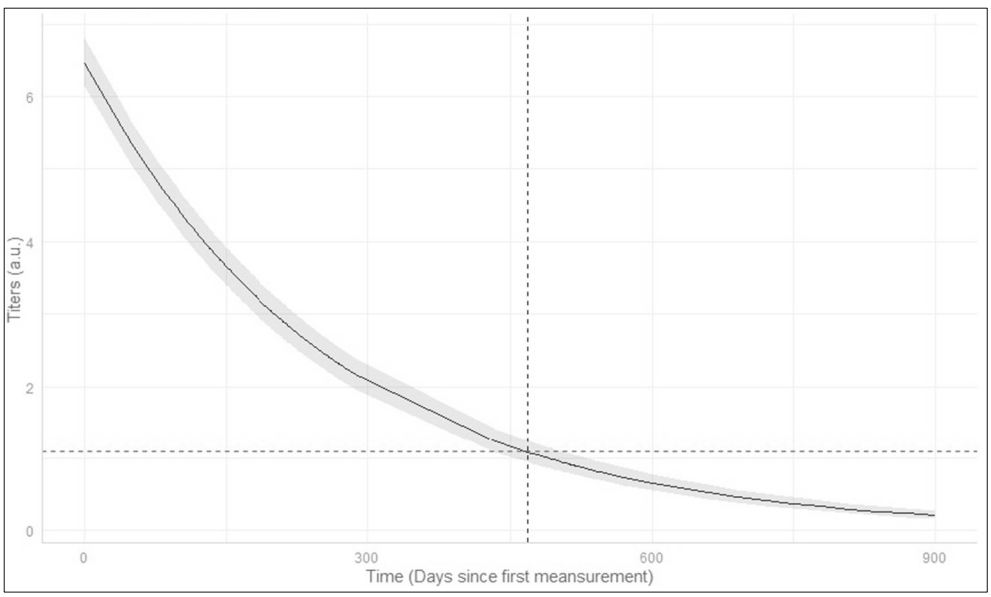

Figure 1 Evolution of anti-SARS-CoV-2 titers over time. Linear mixed model for the SARS-CoV-2 IgG antibodies decline, with the overall mean trajectory from the mean baseline level. The mean trajectory and 95% confidence interval are shown as a solid line and shaded gray area, respectively. The dashed vertical line represents the mean time to loss of antibodies from baseline and the dashed horizontal line represents the titer threshold of 1.1 A.U.

In conclusion, the findings of our research are encouraging, demonstrating a mean durability of naturally acquired antibodies close to 16 months, suggesting a strong protective role against SARS-CoV-2 reinfection.

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Data Availability *The data underlying this article will be shared on reasonable request to the corresponding author.*

Declarations:

Ethics Approval: *The protocol was approved by the Ethics Committee of HM Group (GHM) (Comité Ético de Investigación con Medicamentos de HM Hospitales) (ref. no. 20.04.1611/1640-GHM).*

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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