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Original Article

Assessing COVID IGRA and IgG antibodies in healthcare workers post vaccination

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Abstract

Introduction: This study evaluated the durability of humoral and cell-mediated immunity (CMI) post Pfizer vaccination among healthcare workers (HCWs) at a tertiary care center in Lebanon.

Methodology: A total of 42 HCWs were enrolled, with their past infection and/or vaccination duration ranging between 2 months and 2 years. Blood samples were tested for COVID CMI and humoral immunity simultaneously. Testing for COVID CMI was done by measuring the interferon gamma-release assay (IGRA) using the QuantiFERON SARS-CoV-2 test, and for COVID humoral immunity using the lateral flow Cellex qSARS-CoV-2 IgG/IgM Rapid Test.

Results: The study group was 69% female and 31% male, aged 22–51 years. SARS-CoV-2 was contracted by 33 (78%) HCWs. Positive COVID humoral IgG and CMI response were found among 35 (83.3%) and 19 (45.2%) HCWs, respectively. Combining the findings for both tests revealed concordant positivity in 35.7%, concordant negativity in 7.1%, Pos IgG – Neg IGRA in 47.6%, and Neg IgG – Pos IGRA in 9.5%.

Conclusions: Generally, no correlation was established between humoral and CMI responses following COVID-19 vaccination. That only 83.3% and 45.2% among the Pfizer-vaccinated HCWs tested positive for COVID humoral and CMI, respectively, prevents substantial conclusions about test reliability for determining immunity status post vaccination. Whether these results are influenced by the specific antigenic epitopes used in the tests or by the potential deterioration of the immune response over time remains to be determined. The incongruity between humoral and CMI responses post-vaccination suggests the need for more comprehensive testing methodologies to assess post-vaccination immunity.

Key words: COVID-19; humoral immunity; cell-mediated immunity.

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Introduction

As soon as COVID-19 virus was declared a pandemic, research activity was initiated globally in an unprecedented manner to better understand the disease including the rapid development of vaccines and therapies, as well as determination of the duration of protection provided by these interventions [1,2]. Immunization against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) through developed vaccines that potentiates the immune response (IR) proved being essential and remains the best preventative measure to reduce the risk of severe illness, morbidity, and mortality from this infection [3].

It is well known that post pathogen exposure, both humoral and cell-mediated immunity (CMI) are mobilized [4,5]. Yet, follow-up and monitoring post COVID-19 infection and vaccination remains unsettled regarding durability of humoral and CMI in response to the different SARS-CoV-2 variants and vaccine types [6].

Several studies were conducted to assess and follow up the durability of the COVID-19 humoral immunity in HCWs, a group that showed a remarkable incidence of COVID-19 infection during the pandemic [7]. For example, Lumley *et al*. and Morgiel *et al*. reported that following vaccination, the humoral immunity was maintained for 6–9 months [8,9]. Other studies concluded that past infection provided a stronger and more prolonged humoral immunity, persisting for up to 12 months [10-13].

From an immunological perspective, the durability of humoral immunity after natural infection or vaccination wanes over time and protection is ensured through CMI. This is particularly due to memory poly-specific T cells and conservation of T cell epitopes between variants of concern (VOCs) [14,15].

The assessment of T-cell-mediated immunity against SARS-CoV-2 is believed to offer a glimpse into protection from severe COVID-19, and acts as a source for optimizing COVID-19 vaccine design since some studies showed that CMI was stable for 9 months

[16,17]. While T cells are a major contributor in tackling infections, studies assessing CMI post COVID-19 infection and vaccination are scarce. One such study was conducted by Ni *et al*. to assess both humoral and CMI responses in individuals recovering from COVID-19 to understand the protective immunity developed after infection and found that the presence of SARS-CoV-2-specific antibodies corresponded with robust T cell responses, detected by flow cytometry, highlighting the interplay between both humoral and CMI responses in achieving effective and lasting immunity [18]. This scarcity is largely attributed to flow cytometric techniques being more time-consuming and expensive than measuring anti-SARS-CoV-2 antibodies [19]. Consequently, the novel utilization of Interferon Gamma Release Assay (IGRA) was presented as a promising method to assess CMI against SARS-CoV-2 [20]. However, Kurteva *et al*. reported that while IGRA tests are an excellent tool for evaluating the IR few weeks following vaccination, their effectiveness for assessing the long-term IR is debatable [21]. This above-mentioned information highlights the need for further research on long- term on humoral and CMI post COVID vaccination.

Lebanon was one of the first countries in the Middle East region to experience critical COVID-19 outbreaks and multiple waves of infections that heavily impacted the healthcare system leading to high infection rates among HCWs who were prioritized for vaccination efforts [22]. In Lebanon, though few studies addressed different aspects of COVID-19, none has evaluated the durability of humoral and CMI responses post Pfizer vaccination among HCWs, thus warranting this study.

Methodology

Study population and enrollment criteria

The study was conducted during the period of 1 March 2023 to 31 May 2023, enrolling 42 HCWs at the American University of Beirut Medical Center (AUBMC). Inclusion criteria were being less than 55 years old, vaccinated at least two doses of the Pfizer vaccine, not infected nor in contact with a person infected with SARS-CoV-2 in the past 60 days, being free of chronic diseases and chronic medications. Recruitment was voluntary, and participants were approached from various departments within the hospital to ensure a diverse sample of HCWs. Upon enrollment, participants were questioned to document the following: age, gender, dates of administration of the Pfizer vaccine, history of documented past COVID-19 infections and the corresponding dates of infection.

Laboratory testing and analysis methods

The Cov CMI was assessed by measuring IGRA using the QuantiFERON SARS-CoV-2 test (RUO Qiagen, Hilden, Germany), selected for its easier accessibility and better durability in assessing CMI and was the only one available in our market. Briefly, whole blood was drawn from each participant to fill up the four tubes in the kit which included SARS-CoV-2 antigen1 (Ag 1), SARS-CoV-2 antigen2 (Ag 2), mitogen, and nil tube. Ag1 targets the spike protein of SARS-CoV2, while Ag 2 targets the nucleocapsid protein. The tubes were incubated at 37°C for 16–20 hours, after which they were centrifuged and the plasma from each was removed and tested by ELISA to measure the released amount of interferon gamma (IFN-γ). Positive results were calculated based on a cut-off value of Ag1 minus nil or Ag2 minus nil being ≥ 0.35 IU/mL or ≥ 25% of nil value, in the settings of having a nil ≤ 8 IU/mL.

For Cov humoral immunity determination, an additional blood sample was simultaneously taken from each HCW from the blood drawn as above. The serum from this sample was used to measure the specific IgG antibody response using the lateral flow Cellex qSARS-CoV-2 IgG/IgM Rapid Test (Cellex, NC, USA), selected for its availability, ease of use, and validated reliability in our College of American Pathologists (CAP) accredited laboratory to detect IgG antibodies against the spike protein. Both tests were conducted according to manufacturers' instructions in the serology division of the Department of Pathology and Laboratory Medicine at AUBMC. Finally, statistical analysis was carried out using the IBM SPSS Statistics version 29.0, September 2023.

Table 1. Study group demographics.

Characteristics	n (%)
Sex	
Female	29 (69)
Male	13 (31)
Age (years)	
< 30	22 (52.4)
30-40	10 (23.8)
> 40	10 (23.4)
No. COVID infections	
0	9 (21.4)
1	22 (52.4)
2	9 (21.4)
3	2 (4.8)
No. vaccine doses	
2	16 (38.1)
3	25 (59.5)
4	1 (2.4)

Results

Demographic characteristics

The study population was comprised of 42 HCWs (69% female and 31% male). The age distribution of the participants was as follows: 76.25% below 40 years and 23.4% above 40 years. Regarding past infection with COVID-19, 21.4% reported no prior infection, 52.4% had been infected once, 21.4% had been infected twice, and 4.8% had been infected three times. In terms of number of vaccine doses, 38.1% received two doses, 59.5% received three doses, and 2.4% received four doses (Table 1).

Cov humoral and CMI response

Table 2 shows the Cov IgG and CMI responses among the HCWs. IgG positivity was observed in 84% of the participants. In contrast, only 45% of the participants tested positive for IGRA. Regarding the combined test results of Cov IGRA and IgG, 35.7% of the participants tested positive for both tests, 47.6% tested positive for IgG but negative for IGRA, 9.5% tested negative for IgG but positive for IGRA, and 7.1% tested negative for both tests. The Kappa measure of agreement between the two tests was zero, indicating no agreement beyond what would be expected by chance.

Correlation of IGRA antigens with COVID IgG serostatus

Correlation of test results between IGRA antigens as relates to COVID IgG serostatus revealed variable results among the 42 tested HCWs. Among those positive for both Ag1 and Ag2, 21.4% tested positive for COVID IgG, while 2.3% tested negative. For individuals who tested positive for Ag1 but negative for Ag2, 2.3% had positive COVID IgG, with none testing negative. Among those negative for Ag1 but positive for Ag2, 11.9% tested positive for COVID IgG, and 7.1% tested negative. Finally, among those negative for both Ag1 and Ag2, 47.6% tested positive for COVID IgG, and 7.1% tested negative (Table 3).

Association with demographic factors

Age

With respect to age, there was a statistically significant difference between those who were below 40 years and above 40 years (p value = 0.034), whereby 87.5% of participants aged below 40 years tested positive for IgG compared to 70% positivity in those older than 40 years. However, 50% of those aged below 40 years tested positive for IGRA in comparison to 30% of those whose aged above 40 years (p = 0.676).

Table 3. Correlation between IGRA antigens and COVID IgG result among the 42 tested individuals.

IGRA COV Ag	COV IgG n (%)	
	Pos	Neg
Pos Ag1 - Pos Ag2	9 (21.4)	1 (2.3)
Pos Ag1 - Neg Ag2	1 (2.3)	0 (0)
Neg Ag1 - Pos Ag2	5 (11.9)	3 (7.1)
Neg Ag1 - Neg Ag2	20 (47.6)	3 (7.1)

Gender

With respect to gender, no significant difference in Cov IgG positivity was found between males (84.6%) and females (82.7%) (p = 0.881). Similarly, the positivity rate for the IGRA test did not differ significantly between males (46%) and females (44.8%) (p = 0.936).

Association with infection history

With respect to the number of prior infections, there was no significant difference in IgG test positivity across different infection histories (p = 0.841). Specifically, those with no prior infections had an 88.9% positivity rate, those with a single infection had an 81.8% positivity rate, and those with two prior infections had a 77.8% positivity rate, while those with three infections had a 100% positivity rate. For IGRA test outcomes, positivity rates varied with infection history: 22.2% positivity for no prior infections, 50% for one infection, 55.6% for two infections, and 50% for three infections. None of these differences was statistically significant (p = 0.47).

Association with vaccination history

With respect to the number of vaccine doses, IgG test positivity varied with the number of vaccine doses: 68.75% among those who received two doses, 92% among those who received three doses, and 100% among those who received four doses. Additionally, IGRA test outcomes also varied with vaccination status with 37.5% positivity for two doses, 52% for three doses, and 100% for four doses. None of these

Table 2. Qualitative comparisons between IGRA-SARS and COVID IgG among 42 tested individuals.

IgG test	IGRA test n (%)			Kappa
	Positive	Negative	Total	
Positive	15 (35.7)	20 (47.6)	35 (83.3)	
Negative	4 (9.5)	3 (7.1)	7 (16.6)	0
Total	19 (45.2)	23 (54.7)	42 (100)	

differences was statistically significant. (p = 0.135 and 0.433, respectively).

Duration since last vaccine dose

The average time since the last vaccine dose was about 382 days (SD = 175.6 days), ranging from 60 to 760 days. Participants with positive IgG results had an average rank of 20.23, compared to an average rank of 27.86 for those with negative results, indicating that those with negative IgG, on average, had a slightly longer time since their last vaccine dose compared to those with positive results. For IGRA testing, participants with positive results had an average rank of 17.5, while those with negative results had a mean rank of 24.8, indicating that participants with negative IGRA results, on average, had a slightly longer time since their last dose compared to those with positive results. However, the time from the last vaccine dose to the day of testing was not statistically significant for either humoral or CMI test outcomes (p = 0.14 and 0.054, respectively). Therefore, it cannot be definitively concluded that a longer time since the last vaccine dose is associated with a positive or negative result for IgG and IGRA tests.

Discussion

Lebanon faced multiple waves of SARS-CoV-2 and reported high incidence rates of infection even among vaccinated HCWs especially due to emergence of new variants and lack of understanding the role of the IR to the virus [23].

This study addressed the unresolved specific humoral and CMI responses durability among 42 HCWs after SARS-CoV-2 vaccination with or without previous infection. The positivity of 83.3% for COVID-19 IgG and 45.2% for COVID-19 IGRA in our study varied compared to the positivity reported by others in a similar study population. Example of the latter is reflected in a study conducted by Schiffner *et al*. in Germany where IgG was positive in 76.6% and IGRA was positive in 66.5% of the participants [24]. These differences could be attributed to different variables that could affect the COVID-19 IR including age, gender, number of previous infections, number of received vaccinations, and time elapsed since the last vaccine dose. Differences between our findings and those of other studies could be attributed to variations in population characteristics, vaccine types, and testing methodologies.

Regarding age, HCWs under 40 years had a higher rate of positive IgG results (87.5%) compared to those over 40 years (70%) (p = 0.034). Such findings align with the concept of immune senescence, where vaccine responses tend to weaken in older individuals [25]. However, this remains debatable as suggested by Fernandes *et al*., who reported no significant association between age and humoral immunity following vaccination [26]. In contrast, Zeng *et al*. found that younger individuals had more vulnerable humoral immunity and shorter protection duration than older individuals [27]. This contradiction between this study and ours could be due to the discrepancy in population demographics and vaccination history, especially that Zeng *et al*. conducted their study on convalescent COVID-19 patients in Wuhan who had recovered for 1 year regardless of their vaccination status [27].

Regarding IGRA, our results indicated that age did not impact the test outcomes. Similarly, gender did not play a significant influence on the positivity of either IgG or IGRA tests. In this context, our findings go along those reported by Salvagno *et al*. who assessed humoral and cellular immunity after vaccination in HCWs and reported that demographic factors, including gender and age, were not predictors of either type of response [20].

Concerning the number of prior infections and vaccinations, these factors did not significantly impact the positivity rate of IgG and IGRA test results in our study. Lee *et al*. reported high incidence rates of infection even among vaccinated HCWs [28]. This could be attributed to waning vaccine-induced immunity and the emergence of new variants [23,28]. In contrast, Zurac *et al*., Chivu-Economescu *et al*., and Zhong *et al*. have previously demonstrated that better protection is conferred by vaccination in individuals who have contracted COVID-19 infection in comparison with those who have only received two doses [29-31]. This is because the infection allows them to develop more broadly neutralizing and persistent antibodies, along with a stronger CMI [29-31]. In line with these findings, Ferrari *et al*. and Pitiriga *et al*. have respectively reported that humoral and CMI responses were more durable in vaccinated individuals with a history of COVID-19 [16,17]. Whether this deteriorated immunity is due to the type of antigenic epitopes used for detecting the IR or the waning of the IR over time remains to be determined.

Regarding the effect of time on testing the humoral and CMI response post vaccination or infection, variable results have been reported [32]. In our study, time was found to have no significant effect on the waning of IgG levels and T cell response up to 14 months. However, a systematic review and meta-

regression study by Bobrovitz *et al*. reported that immunity wanes over time, often within months [33].

The simultaneous testing results for IgG and IGRA were found to be heterogeneous in our study and in other studies. Remarkably, we observed a lack of agreement between the performed IgG and IGRA tests, especially that 47.6% tested positive for IgG but negative for IGRA, and 9.5% tested positive for IGRA but negative for IgG. These discrepant findings could be attributed to the high IGRA cut-off value set by the manufacturer's guidelines, indicating a need for optimization to yield more relevant and precise values for CMI. This concurs with the proposal of Vogrig *et al*., who conducted a similar assessment and suggested lowering the cut-off values established for humoral and cellular assays in their tested kits [34]. Similarly, Kurteva *et al*. recommended a cut-off between 0.15 and 0.2 IU/mL for the IGRA test and recommended performing the test few weeks after vaccination and even questioned its utilization for long-term CMI assessment[21]. This is because antigen-specific T cells that secrete IFNγ are initially observed in the blood upon stimulation but later localize to the lymph nodes, continuously moving between the blood stream and lymph nodes based on functional requirements and stimuli. This dynamic behavior could potentially lead to false-negative IGRA test results [21]. Also, one reason why some HCWs tested negative for IgG but positive for IGRA could be the use of a rapid lateral flow test in our study. Rapid lateral flow tests provide a less sensitive quantification method of SARS-CoV-2 antibodies than automated lab-based assays such as ELISA [35].

Another possible factor to explain the differences in the IR detected among the two test modalities used in our study can be attributed to the type of antigenic epitopes used in these tests. This may clarify the fact that only 83% and 45% of Pfizer-vaccinated HCWs tested positive for COVID-19 humoral and CMI responses, respectively, and thus does not allow us to draw substantial conclusions about the reliability of the tests we used to determine the post COVID-19 vaccination immunity. This can possibly be supported by the lack of consistent agreement in testing results among antigen 1 and antigen 2, whereby eight participant samples tested positive for antigen 2 but negative for antigen 1, and one patient sample tested positive for antigen 1 but negative for antigen 2. The overall findings warrant the need to identify reliable antigenic epitopes to cover for credible testing towards determining the accurate CMI and humoral immunity in SARS-CoV-2 infection.

Limitations and strengths in this study are noted. A few factors that may have affected the robustness of our findings include the small size of the study population, limited age range and predominance of female participants. Besides, the study did not include follow-up assessments at different time intervals, which would have provided a clearer assessment of the durability regarding the IR. However, despite such limitations, this study is among the few reported in the literature that addressed this topic, and to our knowledge, it is the first study to assess CMI using IGRA over a long post-vaccination period (up to 2 years). Also, our findings are particularly noteworthy because the assessment was conducted on healthy individuals, free of any chronic diseases and not infected during the time of the study.

In conclusion, no correlation was established between humoral and CMI responses following COVID-19 vaccination. The fact that only 83.3% and 45.2% among the Pfizer-vaccinated HCWs tested positive for COVID-19 humoral immunity and CMI, respectively, doesn't allow us to draw substantial conclusions about which test is more reliable for determining immunity status post COVID-19 vaccination. Whether these results are influenced by the specific antigenic epitopes used in the tests or by the potential deterioration of the IR overtime remains to be determined. Based on our findings, we recommend optimizing the IGRA cut-off values to obtain more accurate CMI measurement as those specified by the manufacturer seem to be high. For a more accurate measure of long-term immunity, it is essential to adopt an integrated approach that combines both humoral and CMI assays.

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Conflict of interests
No conflict of interests is declared.

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