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Assessment of CD4+, CD8+ T cell and Th1 Cytokine Levels in Healthcare Workers Vaccinated against COVID-19 after the COVAX Initiative in Côte d'Ivoire

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ABSTRACT

The COVID-19 pandemic had urgently required the availability of effective vaccines to stop its spread. Despite reports of the effectiveness of these vaccines, SARS-CoV-2 continued to be transmitted. This raised concerns about the immune response to SARS-CoV-2. Two years after the COVAX initiative in our country, we conducted a study to assess the cellular response induced by vaccination among health workers in Abidjan. This was a cross- sectional study that included 350 health workers. It focused on age, sex, workstation, body mass index, history relating to COVID-19, existence of comorbidity, occupational stress, CD4+ T cell levels and CD8+ and the concentrations of the cytokines IFN-γ, TNF-α, IL-6 and IL-2. CD4+ and CD8+ T cell levels and cytokine titers were determined using the BD FACS CANTO II cytometer. Processing was performed using BD FACSCanto software and the CBA protocol. The population average was 40.65 years. CD8+ T-cell levels were significantly correlated with IFN-γ, TNF-α and IL-2 cytokine concentrations. A history of SARS-CoV-2 infection was significantly associated with CD8+ T cell and Th1 cytokine levels. In conclusion, in healthcare workers, T-cell levels continued to increase in the third trimester after vaccination against COVID-19. Additionally, history of SARS-CoV-2 infection appeared to stimulate the cytotoxic T cell response.

Keywords

COVID-19 vaccination; Healthcare workers; SARS-CoV-2; T Lymphocytes; Th1 Cytokines.

Introduction

Discovered in December 2019, due to cases of pneumonia, SARS-CoV-2 led to an unprecedented COVID-19 pandemic. In response to this pandemic, a number of effective SARS-CoV-2 vaccines have been developed, evaluated and deployed in record time [1]. Studies results highlighted an efficacy of SARS-CoV-2 vaccines. In these studies, high levels of SARS-CoV-2 neutralizing antibodies and strong antigen-specific Th1 cellular responses were reported [2,3]. CD4 T cells cooperate with B cells to produce antibodies and orchestrate the response of other immune cells. CD8+ T lymphocytes kill infected cells to reduce the viral load. Several studies have reported T-cell activation in almost all subjects infected with SARS-CoV-2 [4-6]. SARS-CoV-2 specific CD4+ and CD8+ T cells are reported to have shown the best response

against spike protein and produce Th1 effector cytokines (IFN-γ, TNF-α) in addition to Th2 cytokines (IL-4, IL- 5) and Th17 (IL-17). Th1-type cytokines tend to induce a pro-inflammatory response, while Th2-type cytokines induce an anti-inflammatory response [7]. However, the interaction mechanism of SARS-CoV-2 and the immune response induced are not sufficiently clear [8]. The accurate role of CD4 and CD8 T lymphocytes in the development or protection of COVID-19 is still poorly understood [9]. In addition, an increase in the number of cases of SARS-CoV-2 infection after full vaccination had been mentioned [10].

In Côte d'Ivoire, as part of the COVAX Initiative, four vaccine platforms were deployed throughout the country. These included inactivated whole virus vaccines (Sinovac-Coronavac), mRNA encapsulated in lipid nanoparticles (Pfizer-BNT162b2, Moderna-mRNA 1273) and adenoviral vectors (AstraZeneca-AZD1222, Janssen (Johnson & Johnson)-Ad26.COV2.S) [11]. Health workers who were at the forefront of COVID-19 management had paid a heavy price [12-14]. Like other countries, Côte d'Ivoire has opted for targeted vaccination of its healthcare professionals who constitute a group at risk of infection [14,15]. Two years after the COVAX Initiative, as vaccination continues in our country, a question arises about the immune protection of these healthcare workers. What about the post-vaccination cellular immune response of these workers? We seem to have little, if any, data in Côte d'Ivoire. This study aimed to assess T-cell and Th1 cytokine level in healthcare workers vaccinated against COVID-19 in Abidjan. We determined the quantitative characteristics of SARS-CoV-2-specific T cells and the Th1 cytokine profiles correlated with this response. We then identified the possible parameters likely to influence the levels of these lymphocytes. This could provide valuable insights about the extent of immunity mediated by SARS-CoV-2-specific T cells in health workers in Abidjan.

Materials and Methods

Study type and population

This was a prospective, cross-sectional over three months. It was part of a large-scale project investigating the carriage and immunogenicity of SARS-CoV-2 in healthcare workers. Participants were recruited and sampled at three university hospitals in Abidjan after obtaining their informed consent. Based on the workstation, we determined three levels of exposure risk. (i) Personnel at low risk of exposure: no contact with patients (administrative personnel, etc.); (ii) Personnel at intermediate risk: contact with an unknown or suspected COVID-19 patient; (iii) High-risk personnel: contact with known COVID-19 patients. The population for this study was established from a random sample of 350 health workers vaccinated against COVID-19 as part of the above-mentioned project.

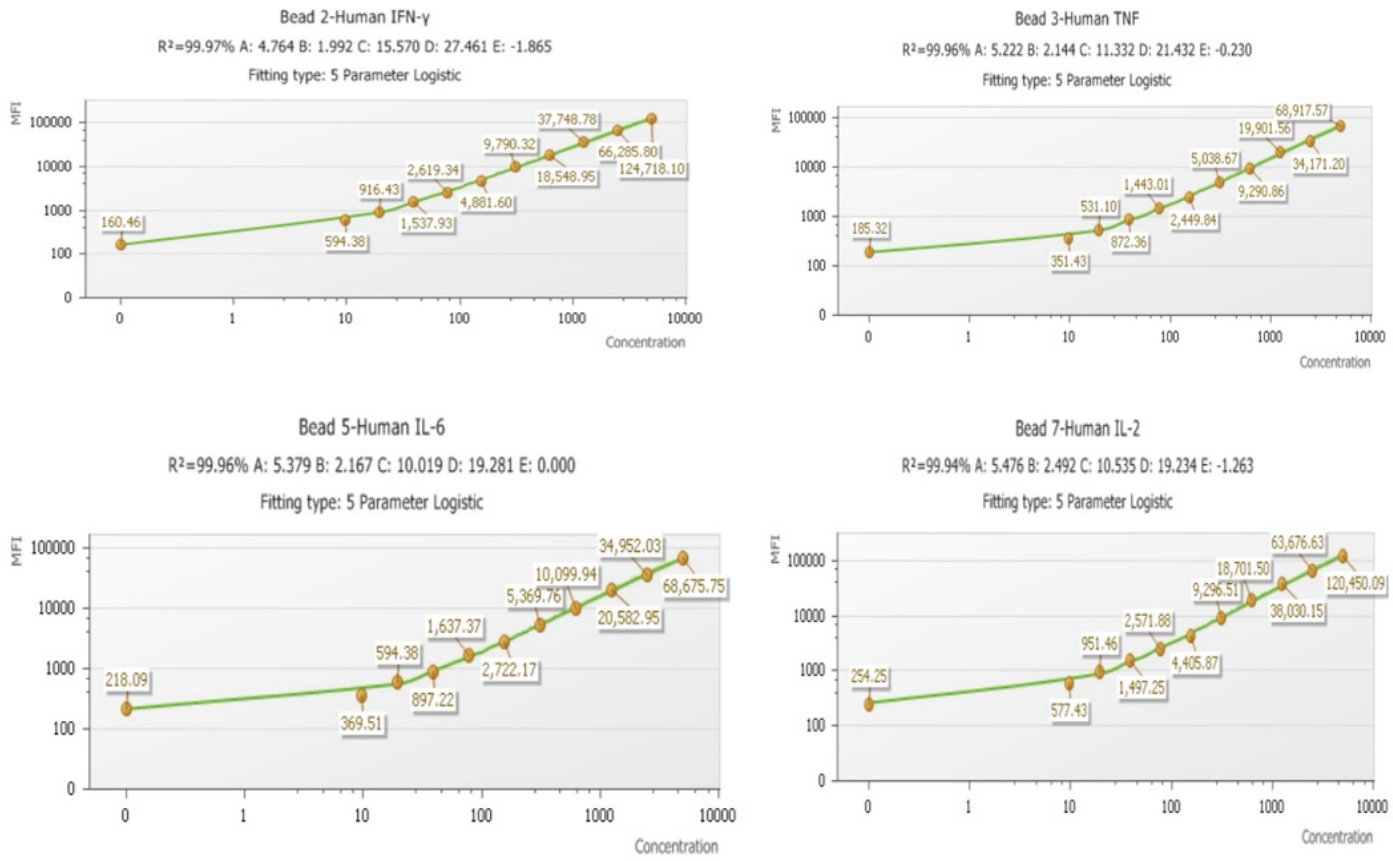

Figure 1: Curves of Human Th1 Cytokine Standards.

Data collection

Epidemiological, clinical, and vaccine-related data were collected using a questionnaire. Blood samples were associated with it (whole blood and serum). This study included the following parameters: age, sex, workstation, body mass index (BMI), COVID-19 history (SARS-CoV-2 infection, vaccination status, name of SARS-CoV-2 vaccination, time between SARS-CoV-2 infection and blood collection, time between vaccination and blood collection), presence of comorbidity (asthma, diabetes, hypertension, sickle cell disease, etc.), the existence of work-related stress due to COVID-19, CD4 and CD8 LT levels and concentrations of the cytokines IFN-γ, TNF-α, IL-6 and IL-2. The history of SARS-CoV-2 infection was justified by the result of a positive RT-PCR test (Reverse Transcription followed by a Polymerase Chain Reaction). Vaccination status and names of vaccines were obtained by checking the agent's vaccination record. Professional stress was assessed by using "The job content questionnaire of KARASEK with 26 items" [16].

Tests carried out

CD4+ and CD8+ T cell levels and cytokines titers were performed using BD FACS CANTO II cytometer (Becton, Dickinson and Company, BD Biosciences, San Jose, CA 95131 USA, Serial Number: V3389002039). The BD CD3/CD8 and CD3/CD4 assays and the 'BD™ CBA Human Th1 Cytokine Kit' comprising three groups of reagents were used. (i) The Bead reagent (Human Capture Beads IL-2, IL-6, TNF, IFN-γ and Cytometer Setup Beads), (ii) Antibody and standards reagent (Human Th1 PE Detection Reagent, Human Th1 Cytokine Standards, PE Positive Control Detector and FITC Positive Control Detector) and (iii) Buffer reagents (Wash Buffer, Assay Diluent and Serum Enhancement Buffer). Lymphocyte count began with lysis of whole blood using BD FACS Lysing Solution, then samples were prepared for immunostaining. Sample processing and analysis was performed using BD FACSCanto software. To determine Th1 cytokine concentrations, we applied the CBA (Cytometric Bead Array) protocol. The principle is based on a method of capturing a soluble analyte or a set of analytes with beads of known size and fluorescence, enabling analytes to be detected using flow cytometry [17]. The CBA protocol was carried out in three steps: (i) preparation of the standards with Human Th1 Cytokine Standards, (ii) preparation of the Mixing Beads with Human Th1 Cytokine Capture Beads reagents and (iii) dilution of the samples. Sample assays and cytometer acquisition were performed on the BD FACS CANTO II. Samples were processed using BD FACSDiva and FCAP Array software. Figure 1 shows the mean fluorescence intensity (MFI) of cytokines.

Ethics approval

This study was approved by « Comité National d'Ethique des Sciences de la Vie et de la Santé (Reference N°: 007-22/MSHPCMU/CNESVS-km) »

Statistical analysis

Statistical analysis was carried out using SPSS V29.0 software. Descriptive and analytical statistical methods were carried out according to the types of variables. Pearson correlation was used to compare two quantitative variables. In cases where the variance is equal and the observations are normally distributed, we used the Student T-test and the Anova test to compare the means of a quantitative variable and a categorical variable. In cases of inequality of variance, we used Mann-Whitney U test. XLSTAT 2023 was used for linear regression. Graphs were obtained using XLSTAT and GraphPad Prism version 9. A p-value < 0.05 was considered as a statistically significant difference.

Results

Descriptive study

The average age was 40.65 years and 54.3% of the participants were overweight with an average BMI of 26.44 kg/m^2. Participants sample was collected on average during the third trimester after vaccination (Table 1). Emergency departments and inpatient departments had the highest number of workers. Pfizer and AstraZeneca vaccines were the most administered vaccines in our population (Table 2).

Table 1: Averages of age, BMI, time between sampling and infection and vaccination.

Parameters	Mean ± SD	Median	Min	Max
Age (year)	40.65 ± 7.97	39.00	25	59
BMI (kg/m^2)	26.44 ± 4.53	25.47	18.49	39.56
Time infection - collection (month)	9.74 ± 5.24	9.00	2	24
Time vaccination – collection (month)	7.95 ± 4.19	7.00	1	26

BMI: Body Mass Index; SD: Standard Deviation; Min: Minimum; Max: Maximum

Table 2: Distribution by workstation and vaccine.

	Rate (percent)
Workstation	
Emergency	92 (26.3)
Hospitalizations	92 (26.3)
Laboratories	76 (21.7)
Consultation Services	54 (15.4)
Administrative Services	22 (6.3)
Other Services	14 (4.0)
Vaccine	
Pfizer	186 (53.1)
Astra Zeneca	122 (34.9)
Johnson & Johnson	14 (4.0)
AstraZeneca/Pfizer	12 (3.4)
Sinopharm	8 (2.3)
AstraZeneca/Moderna	6 (1.7)
Moderna	2 (0.6)

Multiple Correlations

We observed a significant positive correlation between CD4+ and CD8+ T cell levels (Figure 2a). CD8+ T cell concentrations were significantly correlated with those of the cytokine IFN-γ, TNF-α, and IL-2 (Figures 2f, 2g, 2i). The level of TNF-α was significantly correlated with the concentrations of IFN-γ, IL-6 and IL-2 (Figures 2j, 2k, 2l).

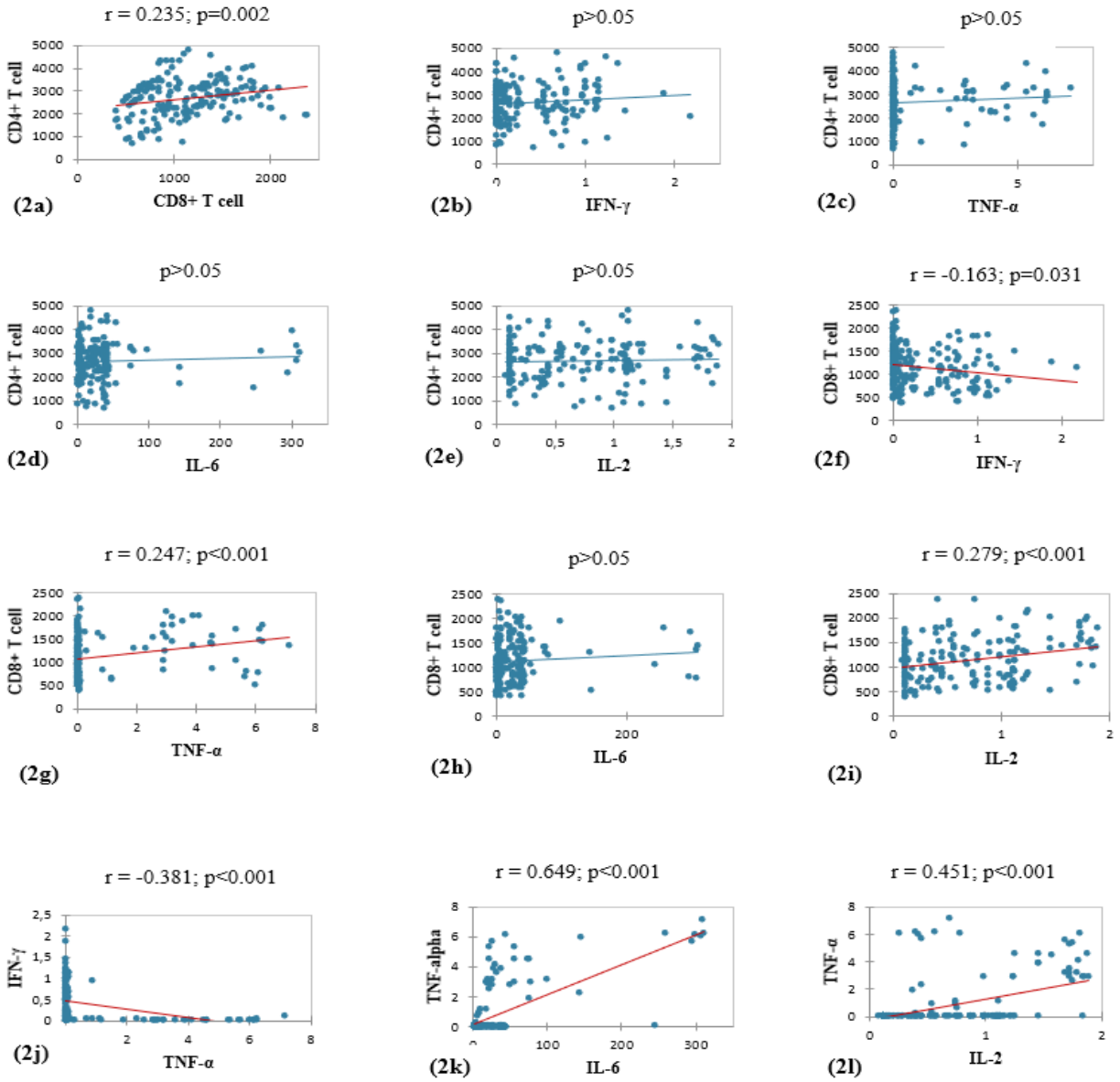

Figure 2: Correlations between T cell subpopulations and cytokines.

Table 3: CD4+ and CD8+ T cells, serum IFN-γ, TNF-α, IL-6 and IL-2 in the global population and No and Present SARS-CoV-2 infection history.

Laboratory parameters	Global population (N = 175)	SARS-CoV-2 infection history		*p value* (No vs. Yes)
		No [n=246 (70.3%)]	Yes [n = 104 (29.7%)]	
CD4+ T cell	2673.74 ± 821.90 [683.84 – 4812.15]	2700.47 ± 836.04	2610.49 ± 791.76	*0.510*
CD8+ T cell	1138.70 ± 441.38 [397.11 – 2378.85]	1042.48 ± 374.97	1366.31 ± 503.18	*< 0.001*
IFN-γ	0.38 ± 0.44 [0.00 – 2.18]	0.52 ± 0.44	0.03 ± 0.13	*< 0.001*
TNF-α	0.83 ± 1.75 [0.00 – 7.15]	0.02 ± 0.03	2.74 ± 2.27	*< 0.001*
IL-6	34.35 ± 57.14 [1.80 – 310.56]	20.77 ± 16.23	66.47 ± 94.95	*0.007*
IL-2	0.70 ± 0.53 [0.08 – 1.89]	0.55 ± 0.43	1.06 ± 0.56	*< 0.001*

Table 4: Comparison between lymphocyte averages and sex, comorbidity, vaccination status and stress.
F: Female; M: Male; I: Incomplete; C: Complete.

(a)		**Gender**		***p value (F vs. M)***
		Female [n=200 (57.1%)]	**Male** [n=150 (42.9%)]	
	CD4+ T-cell (mean ± SD)	2712.81 ± 854.51	2621.63 ± 778.90	*ns*
	CD8+ T-cell (mean ± SD)	1176.84 ± 432.91	1087.84 ± 450.31	*ns*
(b)		**Comorbidity**		***p value (No vs. Yes)***
		No [n= 190 (54.3%)]	**Yes** [n=160 (45.7%)]	
	CD4+ T-cell (mean ± SD)	2689.59 ± 763.71	2654.91 ± 890.62	*ns*
	CD8+ T-cell (mean ± SD)	1127.59 ± 440.70	1151.90 ± 444.61	*ns*
(c)		**Vaccination status**		***p value (I vs. C)***
		Incomplete [n=54 (15.4%)]	**Complete** [n=296 (84.6%)]	
	CD4+ T-cell (mean ± SD)	2530.24 ± 756.61	2699.91 ± 832.99	*ns*
	CD8+ T-cell (mean ± SD)	1199.97 ± 412.54	1127.52 ± 446.86	*ns*
(d)		**Work-related stress in the COVID-19**		***p value (No vs. Yes)***
		No [n=202 (57.7%)]	**Yes** [n=148 (42.3%)]	
	CD4+ T-cell (mean ± SD)	2662.07 ± 826.50	2689.67 ± 820.94	*ns*
	CD8+ T-cell (mean ± SD)	1108.37 ± 436.32	1180.10 ± 419.65	*ns*

Table 5: Comparison between lymphocyte averages and age groups and the risk of exposure linked to the workstation.

	Age range (years)			***p value***
	24 – 36 [n=142 (40.6%)]	**37 – 46** [n=132 (37.7%)]	**≥ 47** [n=76 (21.7%)]	
CD4+ T-cell (mean ± SD)	2728.86 ± 880.92	2673.17 ± 795.76	2571.71 ± 761.35	*ns*
CD8+ T-cell (mean ± SD)	1121.98 ± 437.98	1182.93 ± 463.84	1093.14 ± 411.27	*ns*
	Workstation risk			***p value***
	Low [n=94 (26.9%)]	**Intermediate** [n=168 (48.0%)]	**High** [n=88 (25.1%)]	
CD4+ T-cell (mean ± SD)	2537.62 ± 852.90	2619.38 ± 746.65	2922.91 ± 888.64	*ns*
CD8+ T-cell (mean ± SD)	1158.05 ± 457.59	1108.02 ± 417.04	1176.61 ± 474.25	*ns*

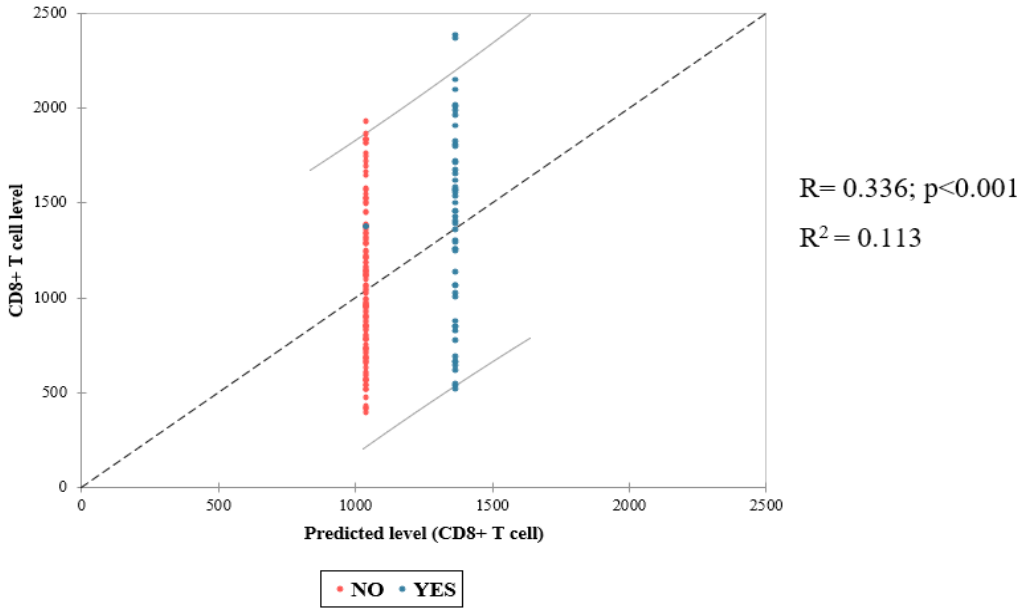

Figure 3: Prediction of CD8+ T-cell levels by history of SARS-CoV-2 infection.

Affecting Factors Study

Comparison of means between T cells and cytokines with SARS-CoV-2 infection history.

Besides CD4+ T cells, we observed a significant relationship between history of SARS-CoV-2 infection and CD8+ T cell and Th1 cytokines (Table 3). Linear regression of CD8+ T cell levels (dependent variable) by history of SARS-CoV-2 infection (explanatory variable) showed a significant correlation between the two variables. Only 11% of the variability in CD8+ T-cell count was explained by a history of SARS-CoV-2 infection. However, the information provided by the explanatory variable is significantly better than what would be explained by the average level of CD8+ T cells (Figure 3).

Comparison of means between T cells and BMI groups, and other parameters

Comparing T-cell averages, we noted a significant link between CD4+ T-cell levels average and body mass index (Figure 4). However, there was no correlation between CD4+ lymphocyte count and BMI (Figure 5). For the other variables included in this study, in comparison with mean lymphocyte concentrations, we found no significant relationship. We noted a female predominance, an absence of stressors and comorbidity in most of our study population. Vaccination was complete in 84.6% of agents (Table 4). Our population was mostly young with a moderate risk of exposure to COVID-19 (Table 5).

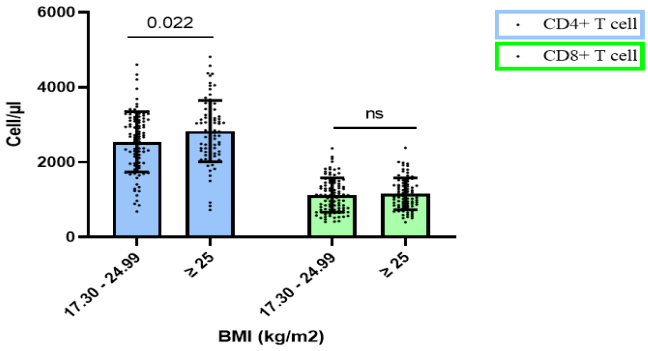

Figure 4: Scatter dot plot CD4 and CD8 T cells according to BMI.

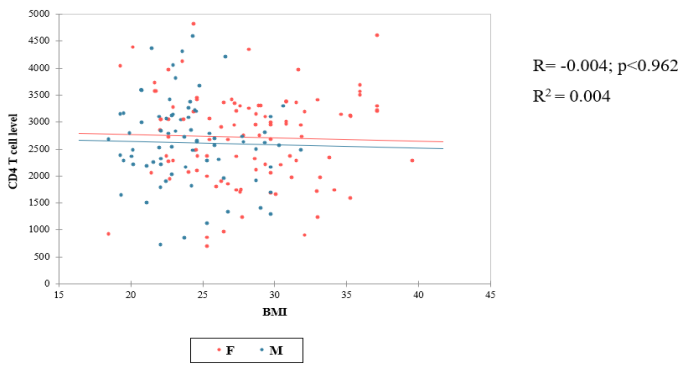

Figure 5: Scatter dot plot CD4 and CD8 T cells according to BMI.

Discussion

As the first available vaccines against SARS-CoV-2 were licensed, healthcare workers became a key target for immunization programs around the world. Two years after the COVAX Facility initiative in Côte d'Ivoire, we wanted to help identify factors that might influence the cellular response to the anti-SARS-CoV-2 vaccine in African subjects. Indeed, following the general model of the adaptive immune response, vaccination should help to control and/or prevent reinfection with SARS-CoV-2. Overall, our study supports the observation of other authors regarding the cellular response following vaccination against SARS-CoV-2 [2,3]. Studies have linked the immunogenicity of various vaccines to the degree of protection against infection or disease [18]. A report including health care workers who were candidates for vaccination in Nigeria, reported a high prevalence of history of SARS-CoV-2 infection (44%) [19]. We recorded a lower percentage (29.7%). Apart from the lack of association with mean CD4+ T-cell levels, we found significant associations between history of SARS-CoV-2 infection compared to mean CD8+ T-cell levels and most pro-inflammatory cytokines. In addition, we observed significant correlations between CD4+ and CD8+ T cell levels on the one hand, and between CD8 T cells and the main Th1 cytokines on the other. CD4+ T cell responses play an important role in the induction of cellular and humoral responses. Our results suggest that COVID-19 vaccines induce a coordinated cellular response by CD4+ T cells, which secrete Th1 cytokines to stimulate and activate CD8+ T cell cytotoxicity. Cytokines are protein mediators that provide critical signals for cell proliferation and inflammation [20]. Healthcare workers with a history of SARS-CoV-2 infection developed a greater cytotoxic CD8+ T response. Vaccination appears to enhance cytotoxic cellular immunity in these individuals. In our series, we did not observe significant difference between the different vaccines. Most vaccines target the SARS-CoV-2 spike protein S. There was no significant association between vaccine status and cellular response in our study. However, studies have shown that the first vaccine dose induces Spike-specific CD4+ T cell responses capable of producing IL-2, IFN-γ and TNF-α [21-23]. In contrast, CD8+ T cell responses become more evident after the second dose [21]. Several factors may contribute to the heterogeneity of immune responses to SARS-CoV-2 [24]. Our population was moderately overweight on average. Agents with a normal body mass index appeared to develop a greater CD4+ T cell response. Reports on the humoral response mention a significant link between BMI and anti-SARS-CoV-2 antibody concentrations [25,26]. Apart from BMI, all parameters included in our series, especially age, comorbidity, and stress, showed no significant relationship with the level of T cell response. A previous study on adaptive immune responses induced by the anti-SARS-CoV-2 mRNA vaccine reported an association between age and T-cell response [22]. Other studies have also linked these parameters to the immune response, in particular the humoral response. In a report on healthcare workers after vaccination with BNT162b2 mRNA against COVID-19, Terpos et al. observed that female sex and young age are predisposed to a more intense immune response [27]. Pellini et al. reported a more intense humoral response in among young and females following vaccination with

the BNT162b2 vaccine in healthcare workers [25]. People with diabetes, hypertension or hematologic disease have been reported to have reduced immune response after vaccination [28,29]. An association between stress and reduced immune defences has been reported, but the mechanisms involved remain unclear [30-32].

This study has some limitations that would have further elucidated the cellular vaccine response to SARS-CoV-2. The sample size may have influenced the results obtained. Although our sample was collected an average of 8 months after vaccination, a long-term longitudinal study would place more emphasis in assessing the persistence of the cellular response. Study of memory T lymphocyte subpopulations would have provided an insight into the level of protection afforded by vaccination in healthcare workers. The lack of analysis of Th2 profile cytokines also does not allow the assessment of the cooperation between T and B lymphocytes.

Conclusion

The results of this study showed that after vaccination with COVID-19, T-cell levels continued to increase during the third trimester. A history of SARS-CoV-2 infection appeared to enhance the cytotoxic T cell response. Ongoing observational studies are needed to determine: (i) Whether durable protection can be achieved; (ii) How long T cells can provide a durable protection; (iii) And whether there is a need to boost vaccination with COVID-19. It is also necessary to monitor the long-term immunity in healthcare workers.

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