International Journal of Immunology Research

Dr. Adou Adjoumanvoulé Honoré
Immunology Laboratory, Felix Houphouët-Boigny (FHB) University, Abidjan, Côte d'Ivoire

Yeboah Oppong Richard
Immunology Laboratory, Felix Houphouët-Boigny (FHB) University, Abidjan, Côte d'Ivoire

Kouacou Amah Patricia
Immunology Laboratory, Felix Houphouët-Boigny (FHB) University, Abidjan, Côte d'Ivoire

Assi Aya Ursule
Immunology Laboratory, Felix Houphouët-Boigny (FHB) University, Abidjan, Côte d'Ivoire

Seri Yida Jocelyne
Immunology Laboratory, Felix Houphouët-Boigny (FHB) University, Abidjan, Côte d'Ivoire

Memel Roselle Charline
Immunology Laboratory of Bouake, Côte d'Ivoire

Moussa Salimata
Blood Transfusion National Center, Côte d'Ivoire

OURA Doris
Blood Transfusion National Center, Côte d'Ivoire

Koffi Adjo Melissa
Cocody Hospital, Côte d'Ivoire

Bathily Maïmouna Sidibé
Mother-Child Hospital, Côte d'Ivoire

Koya Hebert
Immunology Laboratory of Bouake, Côte d'Ivoire

Corresponding Author:
Dr. Adou Adjoumanvoulé Honoré
Immunology Laboratory, Felix Houphouët-Boigny (FHB) University, Abidjan, Côte d'Ivoire

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

Dr. Adou Adjoumanvoulé Honoré, Yeboah Oppong Richard, Kouacou Amah Patricia, Assi Aya Ursule, Seri Yida Jocelyne, Memel Roselle Charline, Moussa Salimata, OURA Doris, Koffi Adjo Melissa, Bathily Maïmouna Sidibé and Koya Hebert

DOI: https://doi.org/10.33545/26648865.2023.v5.i2a.19

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 FACSC anto software and the CBA protocol. The average age of the population 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: SARS-CoV-2, COVID-19, vaccination, healthcare workers, T-cell, 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, multicentre study 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.

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.

Ethics approval
This study was approved by « Comité National d'Ethique des Sciences de la Vie et de la Santé (N° référence: 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.
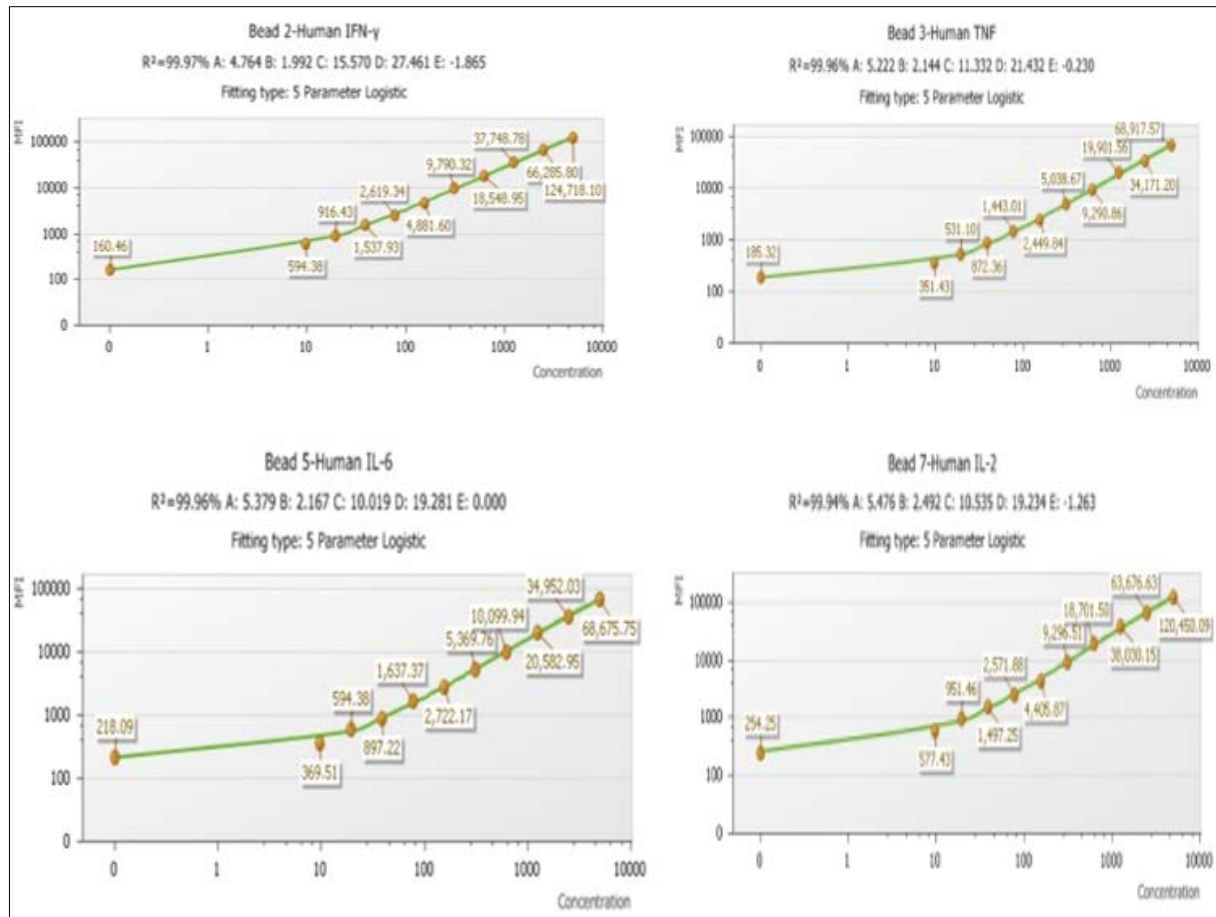
Fig 1: Curves of Human Th1 Cytokine Standards (showing the mean fluorescence intensity (MFI) of cytokines).

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/m². Participants sample was collected on average during the third trimester after vaccination (Table 1).

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/m²)	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

Emergency departments and inpatient departments had the highest number of workers (26.3% in each case). Pfizer and AstraZeneca vaccines were the most administered vaccines in our population, 53.1% and 34.9% respectively (Table 2).

Table 2: Distribution by workstation and vaccine

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).
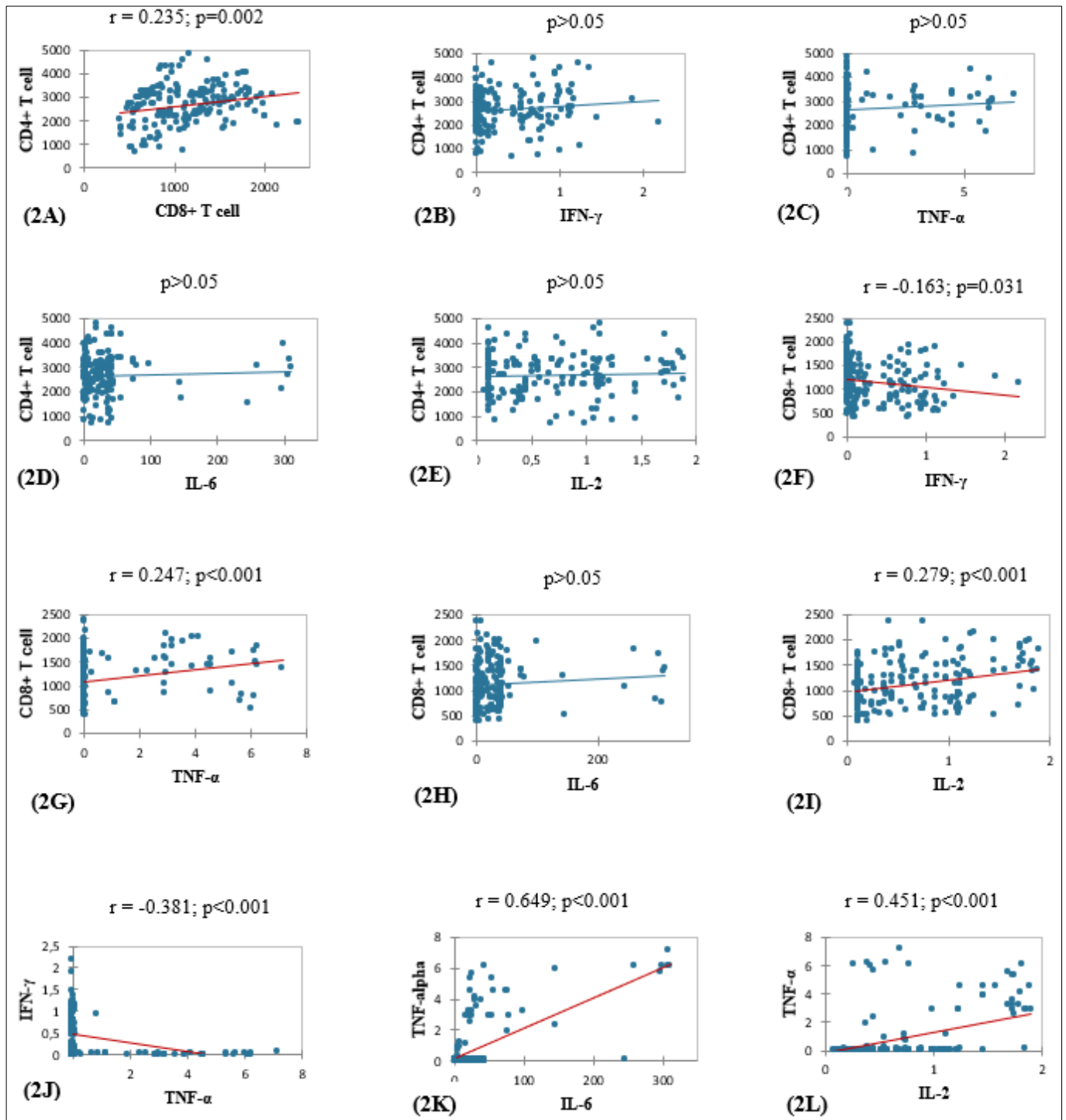

Fig 2: Correlations between T cell subpopulations and cytokines

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 (Table 4 and figure 3).

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

Modelling of CD8+ T-cell concentration explained by history of SARS-CoV-2 infection.
Pearson correlation: R= 0.336; $p<0.001$
$R^2 = 0.113$

Table 4: CD8+ T cell Model Parameters

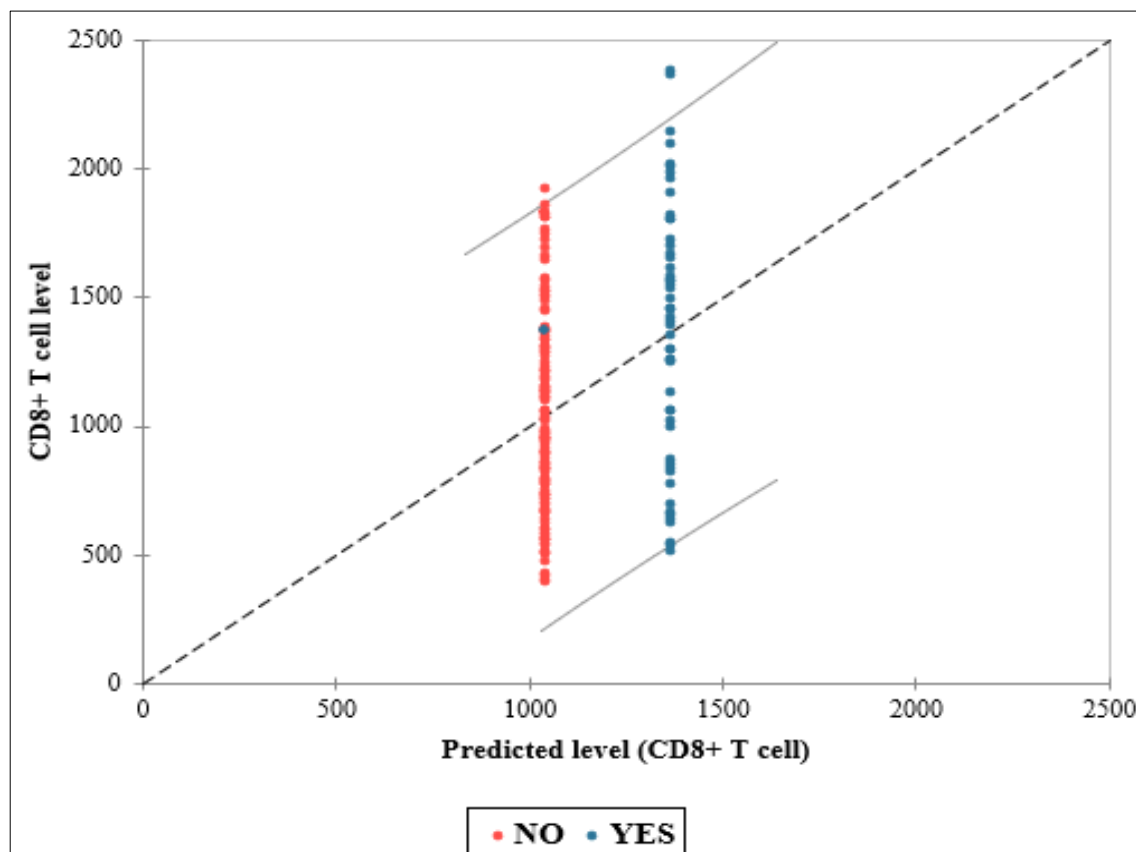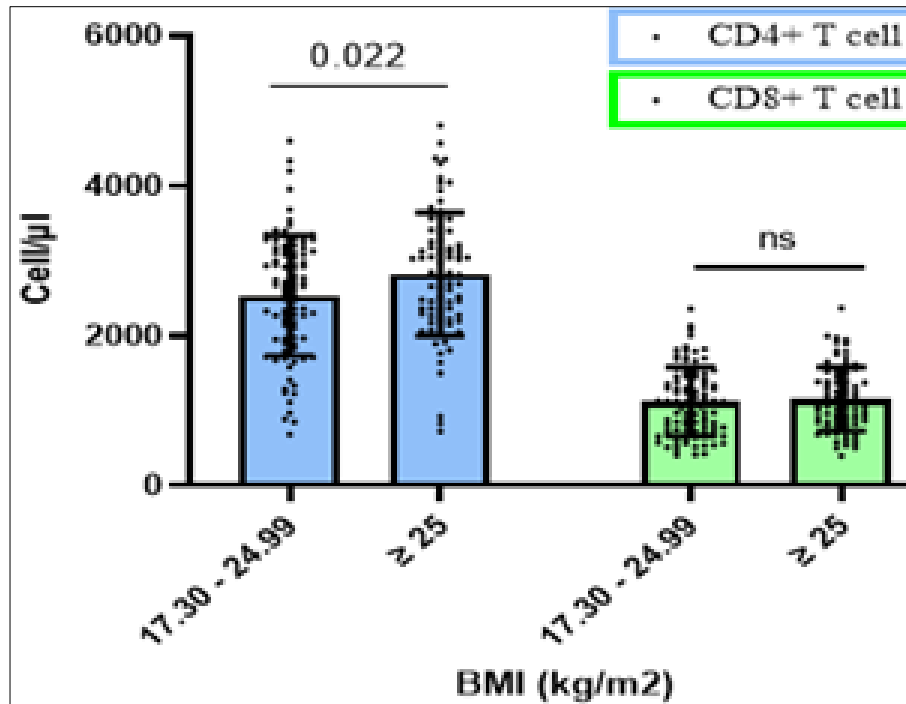| Model	Value	t	p-value	95% CI
Constante	1366.308	23.634	< 0.001	1252.202 to 1480.415
SARS-CoV-2 Infection history-NO	-323.831	4.696	< 0.001	-459.937 to -187.725
SARS-CoV-2 Infection history-YES	0.000			

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

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 (Table 5 and 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 (57.1%), an absence of stressors (57.7%) and of comorbidity (54.3%) in most of our study population. Vaccination was complete in 84.6% of agents (Table 6). Our population was mostly young (40.6%) with a moderate risk (48.0%) of exposure to COVID-19 (Table 7).

Ns: not significant

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

Modelling of CD4 T-cell concentration explained by BMI
Pearson correlation: R= -0.004; *p<0.962*

Table 5: CD4 T cell Model Parameters

Model	Value	t	p-value	95% CI
Constante	2772.767	7.240	< 0.0001	2016.867 – 3528.666
BMI	6.259	-0.407	0.684	-36.582 – 24.063
Gender-Female	116.343	0.829	0.408	-160.666 – 393.353
Gender-Male	0.000			
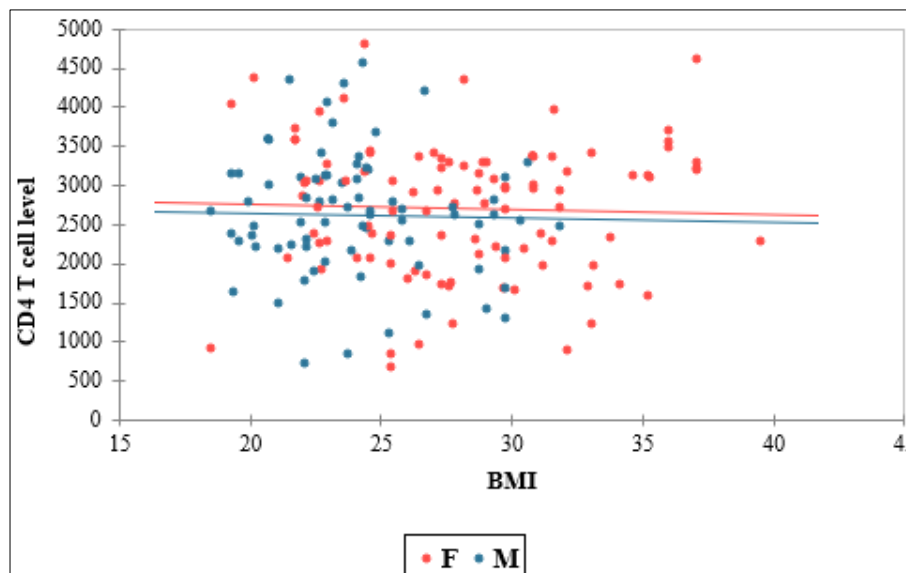
F: Female; M: Male

Fig 5: Down regulation of CD4 T-cell levels by BMI ($R^2 = 0.004$)

Table 6: Comparison between lymphocyte averages and sex, comorbidity, vaccination status and stress

		Gender		p value (F vs. M)
		Female	Male	
(A)		[n=200 (57.1%)]	[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

		Comorbidity		p value (No vs. Yes)
		No	Yes	
(B)		[n= 190 (54.3%)]	[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
		Vaccination status		p value (I vs. C)
		Incomplete	Complete	
(C)		[n=54 (15.4%)]	[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
		Work-related stress in the COVID-19		p value (No vs. Yes)
		No	Yes	
(D)		[n=202 (57.7%)]	[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

F: Female; M: Male; I: Incomplete; C: Complete

Table 7: 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

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 that 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. The majority of 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 of vaccine 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 defenses has been reported, but the mechanisms involved remain unclear [31-32].

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.

Acknowledgments

Conflict of Interest
Not available

Financial Support
Not available

References
1. Addetia A, Crawford KHD, Dingens A, Zhu H, Roychoudhury P, Huang ML, *et al*. Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate. J Clin Microbiol. 21 oct 2020;58(11):e02107-20.
2. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, *et al*. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. Juill 2021;595(7868):572-7.
3. Xu K, Dai L, Gao GF. Humoral and cellular immunity and the safety of COVID-19 vaccines: a summary of data published by 21 May 2021. Int Immunol. 2021 Sept 25;33(10):529-40.
4. Arunachalam PS, Wimmers F, Mok CKP, Perera RAPM, Scott M, Hagan T, *et al*. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. Science. 2020 Sept;369(6508):1210-20.
5. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, *et al*. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020 Nov;587(7833):270-4.
6. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, *et al*. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell. 2020 Jun 25;181(7):1489-1501.e15.
7. Dos Santos WG. Impact of virus genetic variability and host immunity for the success of COVID-19 vaccines. Biomed Pharmacother. 2021;136:111272.

8. Cheng ZJ, Xue M, Zheng P, Lyu J, Zhan Z, Hu H, *et al*. Factors Affecting the Antibody Immunogenicity of Vaccines against SARS-CoV-2: A Focused Review. Vaccines. août 2021;9(8):869.
9. Grigoryan L, Pulendran B. The immunology of SARS-CoV-2 infections and vaccines. Semin Immunol. août 2020;50:101422.
10. Gallais F, Gantner P, Planas D, Solis M, Bruel T, Pierre F, *et al*. Case Report: Evolution of Humoral and Cellular Immunity in Two COVID-19 Breakthrough Infections After BNT162b2 Vaccine. Front Immunol. 2022 Feb 23;13:790212.
11. MSHPCMU. Prévention Covid-19 - Protégeons-nous contre le coronavirus, Ministre de la Santé et de l'Hygiène Publique - Côte d'Ivoire [Internet]. [cité 13 nov 2022]. Disponible sur: http://info-covid19.gouv.ci/welcome/recherches?search=vaccination
12. Mehta S, Machado F, Kwizera A, Papazian L, Moss M, Azoulay É, *et al*. COVID-19: a heavy toll on health-care workers. Lancet Respir Med. 2021;9(3):226-8.
13. Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, *et al*. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health. 2020;5(9):e475-83.
14. OMS. Flambée de maladie à coronavirus (COVID-19) [Internet]. [cité 16 mars 2022]. Disponible sur: https://www.euro.who.int/fr/health-topics/health-emergencies/coronavirus-covid-19
15. WHO. WHO/Europe | Home [Internet]. [cité 13 nov 2022]. Disponible sur: https://www.who.int/europe
16. Questionnaire de Karasek ! Mesure du stress professionnel [Internet]. [cité 30 déc 2022]. Disponible sur: https://www.atousante.com/risques-professionnels/stress-professionnel-questionnaire-karasek/
17. Human Th1/Th2/Th17 CBA Kit [Internet]. [cité 22 déc 2022]. Disponible sur: https://www.bdbiosciences.com/en-ca/products/reagents/immunoassay-reagents/cba/cba-kits/human-th1-th2-th17-cba-kit.560484
18. Naranbhai V, Garcia-Beltran WF, Chang CC, Berrios Mairena C, Thierauf JC, Kirkpatrick G, *et al*. Comparative Immunogenicity and Effectiveness of mRNA-1273, BNT162b2, and Ad26.COV2.S COVID-19 Vaccines. J Infect Dis. 9 déc 2021;225(7):1141-50.
19. Abdullahi A, Oladele D, Owusu M, Kemp SA, Ayorinde J, Salako A, *et al*. SARS-COV-2 antibody responses to AZD1222 vaccination in West Africa. Nat Commun. 17 oct 2022;13(1):6131.
20. Florindo HF, Kleiner R, Vaskovich-Koubi D, Acúrcio RC, Carreira B, Yeini E, *et al*. Immune-mediated approaches against COVID-19. Nat Nanotechnol. août 2020;15(8):630-45.
21. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, *et al*. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature. août 2021;596(7872):410-6.
22. Bai J, Chiba A, Murayama G, Kuga T, Tamura N, Miyake S. Sex, Age, and Ethnic Background Shape Adaptive Immune Responses Induced by the SARS-CoV-2 mRNA Vaccine. Front Immunol. 2022 Mar 28;13:786586.

23. Painter MM, Mathew D, Goel RR, Apostolidis SA, Pattekar A, Kuthuru O, *et al*. Rapid induction of antigen-specific CD4+ T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination. Immunity. 2021 Sept 14;54(9):2133-2142.e3.

24. Bertholom C. Réponse immunitaire associée au Sars-CoV-2. Option/Bio. 2021 Jan;32(627-628):15-7.

25. Pellini R, Venuti A, Pimpinelli F, Abril E, Blandino G, Campo F, *et al*. Initial observations on age, gender, BMI and hypertension in antibody responses to SARS-CoV-2 BNT162b2 vaccine. E Clinical Medicine. 2021 Jun 1;36:100928.

26. Soffer S, Glicksberg BS, Zimlichman E, Efros O, Levin MA, Freeman R, *et al*. The association between obesity and peak antibody titer response in COVID-19 infection. Obesity. 2021;29(9):1547-53.

27. Terpos E, Trougakos IP, Apostolakou F, Charitaki I, Sklirou AD, Mavrianou N, *et al*. Age-dependent and gender-dependent antibody responses against SARS-CoV-2 in health workers and octogenarians after vaccination with the BNT162b2 mRNA vaccine. Am J Hematol. 2021 Jul 1;96(7):E257-9.

28. Lustig Y, Sapir E, Regev-Yochay G, Cohen C, Fluss R, Olmer L, *et al*. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. Lancet Respir Med. 2021 Sept 1;9(9):999-1009.

29. Tawinprai K, Siripongboonsitti T, Porntharukchareon T, Dechates B, Monprach H, Sornsamdang G, *et al*. Persistence of immunogenicity, contributing factors of an immune response, and reactogenicities after a single dose of the ChAdOx1 (AZD1222) COVID-19 vaccine in the Thai population. Hum Vaccines Immunother. 2022 Dec 31;18(1):2035573.

30. Jacque C, Thurin JM. Stress, immunité et physiologie du système nerveux. médecine/sciences. 2002 Nov 1;18(11):1160-6.

31. Padgett DA, Glaser R. How stress influences the immune response. Trends Immunol. 2003 Aug 1;24(8):444-8.

32. Wieduwild E, Girard-Madoux MJ, Quatrini L, Laprie C, Chasson L, Rossignol R, *et al*. β2-adrenergic signals downregulate the innate immune response and reduce host resistance to viral infection. J Exp Med. 2020;217(4).