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Research Article

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T-Cells Levels after Previous Covid-19 Infection and Vaccination in Health Workers in Cote D'ivoire

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Abstract

Justification : *The only means of acquiring protective immunity against SARS-CoV-2 are infection and vaccination. Intensive research is being carried out to understand the similarities and variations in the immune response in naturally recovered patients and after vaccination. Comparing T-cell levels during these two forms of immunisation could provide a better understanding of the cellular immune response induced by each.*

Methods : *This was a descriptive and analytical cross-sectional study on healthcare workers in the 3 hospitals and university centres of Abidjan. A total of 275 regularly assigned health workers were randomly selected for inclusion. Survey forms were completed, vaccination records were consulted for those vaccinated and blood samples were taken. T lymphocyte counts and cytokine assays were performed using flow cytometry. The Kruskal-Wallis test was used to compare the medians.*

Results : *CD4+ counts were significantly higher in vaccinated subjects compared with non-vaccinated subjects and those with a history of infection. On the other hand, CD8+ TL levels were significantly higher in subjects with a history of infection and especially in those with hybrid immunisation compared with those with vaccination as the only type of immunisation.*

In terms of pro-inflammatory cytokines, hybrid immunisation led to an increase in IL-6 and TNF levels. However, IFN levels were lower. In terms of anti-inflammatory cytokines, IL2 levels were higher with hybrid immunisation, but IL-10 levels were lower.

Conclusion : *CD4+ T lymphocyte levels were higher during vaccination and hybrid immunisation, whereas CD8+ T lymphocyte levels were higher during infection and hybrid immunisation.*

Keywords: Covid-19, Adaptive Immunity, T Lymphocytes, Sars-Cov-2, Vaccines

Abreviations

APC : Antigen Presenting Cells
IFN : Interferon
IL : Interleukin
NK : Natural Killer
TL : T Lymphocyte
TNF : Tumor Necrosis Factor

1. Background

Since the outbreak of the disease in Covid-19 in late 2019, numerous studies have been devoted to characterising the innate and adaptive immune responses to SARS-CoV-2 in order to understand

the role of the various immune players in resistance to the disease. In terms of the adaptive immune system, the three main branches studied are B cells (the source of antibodies), CD4+ T cells and CD8+ T cells [1].

During natural infection, CD8+ T cells play an important complementary role in containing infection through their ability to eliminate already infected cells, while CD4+ helper T cells, among other functions, provide signals that support the development of the humoral response [1].

The protective immunity provided by vaccines is essentially based on the production of antibodies and the existence of an immunological memory.

As in other viral infections, T and B cells work in concert with the innate immune system to control SARS-CoV-2. Each adaptive player has distinct response kinetics, antigen recognition mode, effector functions and immunological memory, often in line with theoretical knowledge [2, 3].

However, the response to the SARS-CoV-2 pandemic relied heavily on the development, testing and deployment of vaccines despite the theory of protective herd immunity post-infection with all its risks. In a short space of time, several different vaccine platforms have been developed.

Because of the scale and scope of immunological studies on SARS-CoV-2 in humans, the large number of primary infections, the large number of primary vaccinations and the diversity of Covid-19 vaccines developed in a short space of time, more data are now available on human antigen-specific immune responses to SARS-CoV-2 than to any other acute pathogen [1].

It is now known that the immune response to SARS-CoV-2 can be generated by infection ("natural immunity"), by vaccination ("artificial immunity") or by a so-called hybrid immunity (a combination of the two) [4].

It therefore seems important to study the immune profile of CD4+ T cells and CD8+ T cells, which play an important role in protective cellular immunity against SARS-CoV-2, during Covid-19 infections and vaccinations in our context, in an attempt to understand the best means of protection against this virus.

2. Methods

2.1 Type of Study and Population

We conducted a descriptive and analytical cross-sectional study over a 3-month period (April to June 2022). This study was part of a large project on the carriage and immunogenicity of SARS-CoV-2 in healthcare workers in Côte d'Ivoire. A random sample was taken of all healthcare workers regularly assigned to the three university hospital centres (CHU) in Abidjan-Côte d'Ivoire, from all posts, departments and risk levels combined. All unvaccinated or vaccinated healthcare workers were included in the study, regardless of the type of vaccine and the number of doses already done, and whether or not they had previously been infected with Covid-19. Consent forms detailing the objectives of the study and the advantages and disadvantages of taking part were given to them for their information. We were therefore able to collect 275 health workers who were present at their posts during our survey visits and who agreed to take part in the study after obtaining their informed consent in writing.

2.2 Data Collection

All participants were asked to complete a questionnaire using survey forms to collect information on socio-demographic data, immunisation status, i.e. history of SARS-CoV-2 infection (smptomatic or not, number of infections, etc.) and the notion of vaccination against Covid-19 (dates, type of vaccine, number of doses already received, etc.). Information was collected on the time between infection with SARS-CoV-2 and blood sampling, and the time between vaccination and blood sampling. For a history of SARS-CoV-2 infection, we took into account those who had presented a positive RT-PCR (Real Time-Polymerase Chain Reaction) test result, and for vaccinations, we consulted vaccination records. All respondents were tested for Covid-19 on nasopharyngeal swabs. These samples were used to carry out antigenic tests for Standard Q Covid-19 from SD Biosensor in the presence of the health worker being surveyed, in order to diagnose an ongoing infection. If the test was negative, the health worker was included in the study. Blood samples were taken by venipuncture from the bend of the elbow under vacuum in a vacutainer using EDTA tubes and tubes without anticoagulants for lymphocyte count and cytokine assay, respectively.

2.3 Tests Performed

Total T lymphocyte, CD3+ T lymphocyte, CD4+ T lymphocyte and CD8+ T lymphocyte counts as well as pro- and anti-inflammatory cytokine titers were performed by flow cytometry using BD FACSCanto, BD FACSDiva and FCAP Array software on the BD FACS CANTO II 2-laser cytometer (Reference : CA 95131 USA, series : V3389002039). We performed lymphocyte counts on whole blood using the lysis technique after labelling with antibodies coupled with fluorochromes using the BD CD3/CD8 and CD3/CD4 kit. Pro-inflammatory cytokines (IL-6, TNF and IFN) and anti-inflammatory cytokines (IL-2 and IL-10) were assayed in serum according to the CBA (Cytometric Beat Array) protocol using the BD™ CBA Human Th1/Th2/Th17 Cytokine Kit. The principle of this technique is based on the method of capturing a soluble analyte or a set of analytes with beads of known size and fluorescence, allowing detection of the analytes by flow cytometry.

2.4 Statistical Analysis

Our data were first categorised into 2 main groups : according to the notion of vaccination and according to the notion of previous infection, with internal comparisons. Then, into 4 groups : infected and vaccinated, infected and unvaccinated, uninfected and unvaccinated, and uninfected and vaccinated, with inter-group comparisons.

Microsoft Word and Excel 2011 were used for data entry and table compilation. GraphPad Prism 8 software was used for statistical analysis and to produce figures.

As the data did not pass the various normality tests, we used the non-parametric Kruskal-Wallis test (Anova) to compare the medians at the 5% significance level.

3. Results

Our population was predominantly female, with a sex ratio of 0.68.

The mean time between sampling and the various types of immunisation was 8 months for vaccination and 11 months for Covid-19 infection.

There was a significant difference between the medians of all the parameters analysed in the different study groups.

Generally speaking, there was no difference between the total T-cell counts of vaccinated patients compared with unvaccinated patients and between patients with a history of infection and those without.

On the other hand, there were significant differences in CD4+ T lymphocyte levels between vaccinated patients and non-vaccinated patients, and between infected patients and noninfected patients. Vaccination was the best way of expanding these cells.

In terms of CD8+ LT, there was no difference between the levels of vaccinated patients compared with unvaccinated patients, but there was a significant difference between the levels of infected patients and uninfected patients. Infection, and especially vaccination in patients with a history of infection (hybrid), appeared to be the best means of CD8+ TL expansion.

In terms of pro-inflammatory cytokines, IL-6 and TNF levels were better with hybrid immunisation. However, IFN levels were low with this type of immunisation.

In terms of anti-inflammatory cytokines, IL-2 levels were better with hybrid immunisation. However, IL-10 levels were lower.

4. Discussion

The fight against the Covid-19 pandemic has aroused a great deal of interest in the world of science. Much ink has been spilled over the search for the best means of protection. While some advocated acquiring immunity through vaccination, others opted for herd immunity by infecting larger numbers.

In this study, we enrolled 275 patients, including a high proportion of vaccinated patients, 63.64% (175 patients) who had already received at least one dose of a Covid vaccine, and 106 patients (38.55%) who had at least one Covid-19 infection in their history (Table 1).

		Workforce		History of infection				Vaccination				Symptomatic			
				Yes		No		Yes		No		Yes		No	
	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Enrolled Personnel	275	275	100	106	38,55	169	61,45	175	63,64	100	36,36	69	65,09	37	34,90
Gender Female		163	59,27	79	74,53	84	49,7	100	61,35	63	38,65	52	75,36	15	40,54
Male		112	40,73	27	25,47	85	50,3	75	66,96	37	33,04	17	24,64	22	59,46
p				<0,0001				0,342							

Table 1: Distribution of the General Population According to History of Covid-19 Infection, Clinical Symptoms and Vaccination According to Sex

Women predominated, with a sex ratio of 0.68, although a higher proportion of men (66.96%) than women (61.35%) were vaccinated. The average age was 40.1, making this a relatively young population. 38.55% of the staff had a history of Covid-19 disease. Of these, 65.09% had been symptomatic at the time of the illness, compared with 34.90% who had shown no signs. The disease had only been diagnosed during systematic screening after contact with an infected patient or colleague. This could confirm the hypotheses that the immune system is relatively better able to react to infectious diseases and that the tropical climate has a favourable impact in our African context [5].

These high rates of immunisation acquired both by artificial challenge (vaccination) and by natural challenge (infection) would confer on these staff a kind of collective immunity which could therefore limit the progression of the disease within them.

This favourable immunity, acquired actively, both spontaneously and artificially, could therefore limit contamination of these staff by the SARS-Cov-2 virus, either from patients or among them-

selves, in addition to the significant decline in virus circulation during the study period.

In terms of T lymphocytes (LT), there was a significant difference between the different rates in the different classes, vaccinated or not, whether or not there was a history of Covid-19 infection (Table 2). However, there was no difference between the total lymphocyte levels of vaccinated subjects compared with unvaccinated subjects and infected subjects compared with uninfected subjects (Figure 1A). However, in terms of CD3+ lymphocytes, there was a significant difference (p = 0.0269) between the levels of vaccinated subjects compared with unvaccinated subjects, but no difference between the levels of subjects with and without a history of infection (Figure 1B). This observed difference could also reflect the influence of vaccination on innate immunity cells, including Natural Killer (NK) lymphocytes in general and NKT lymphocytes in particular.

			Covid-19 history		No history of Covid-19		
			Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	P
Overall		275	52	54	123	46	
Median	LT Ttx		5475	5392	5256	5355	0,8869
	CD3		4234	3843	3770	2984	<0,0001
	CD4		1421	1850	2153	1561	<0,0001
	CD8		2270	1874	1498	1257	<0,0001
	IFN		0,0	0,11	0,54	0,26	<0,0001
	TNF		2,9	0,025	0,01	0,99	<0,0001
	IL-2		0,99	0,32	0,45	0,16	<0,0001
	IL-10		0,96	3,2	4,2	1,5	<0,0001

Table 2: Global Comparison of Medians for T Lymphocytes and Cytokines

In terms of CD4+ T lymphocytes, the rate in vaccinated patients was higher than in non-vaccinated patients, with a significant difference (p = 0.0288) (Figure 1 C). In general, this shows a greater expansion of CD4+ T cells in the case of vaccination.

In addition, those with a history of Covid-19 infection had a lower rate compared with the uninfected, with a significant difference (p = 0.0074). That said, CD4+ LT levels are lower after infection than after vaccination. Our observations were in line with those of Xaquin C.D et al who stated in their study that during natural infection, CD8+ LT played an important role in preventing disease progression by eliminating cells already infected, while CD4+ LT played a supporting role in antibody production by secreting cytokines [6]. That said, its expansion would be greater in the event of vaccination. Several other studies have also highlighted the fact that infection with SARS-CoV-2 can cause lymphopenia. Also, because of the possibility of antigenic cross-recognition of T lymphocytes with seasonal coronaviruses and SARS-CoV-2, CD4+ LT specific for SARS-CoV-2 could also be detected in around 40-60% of unexposed individuals [7, 8, 9]. Hence a lower rate in the infected compared with the uninfected. This could also be explained by the action of certain anti-viral cytokines and even a significant activity of innate immunity cells such as NK cells. This could limit the need for a major cytotoxic cellular response.

A higher CD4+ rate in the event of vaccination could also be explained by the fact that most of the vaccines that had been used, and are still being used, had as their main objective the production of neutralising antibodies directed mainly against the virulence antigen of SARS-CoV-2, i.e. the Spike protein. This requires a high level of activity on the part of regulatory cells to orientate the immune response towards a Th2 (T helper 2) profile, i.e. specific humoral immunity to the detriment of cytotoxic-type cellular immunity. Because viral antigens are proteins and not polysaccharides, they cannot be directly recognised by B-LTs to produce antibodies, but this requires cooperation between antigen-presenting cells (APCs) and CD4+ LTs via an HLA-II molecule (MHC-II). That said, the vaccine would specifically induce an expansion of CD4+ TL.

In terms of CD8 LT, we did not find any significant difference between the different rates for vaccinated and unvaccinated patients (Figure 1D). That said, vaccination does not appear here to be a factor that can influence the clonal expansion of these cells.

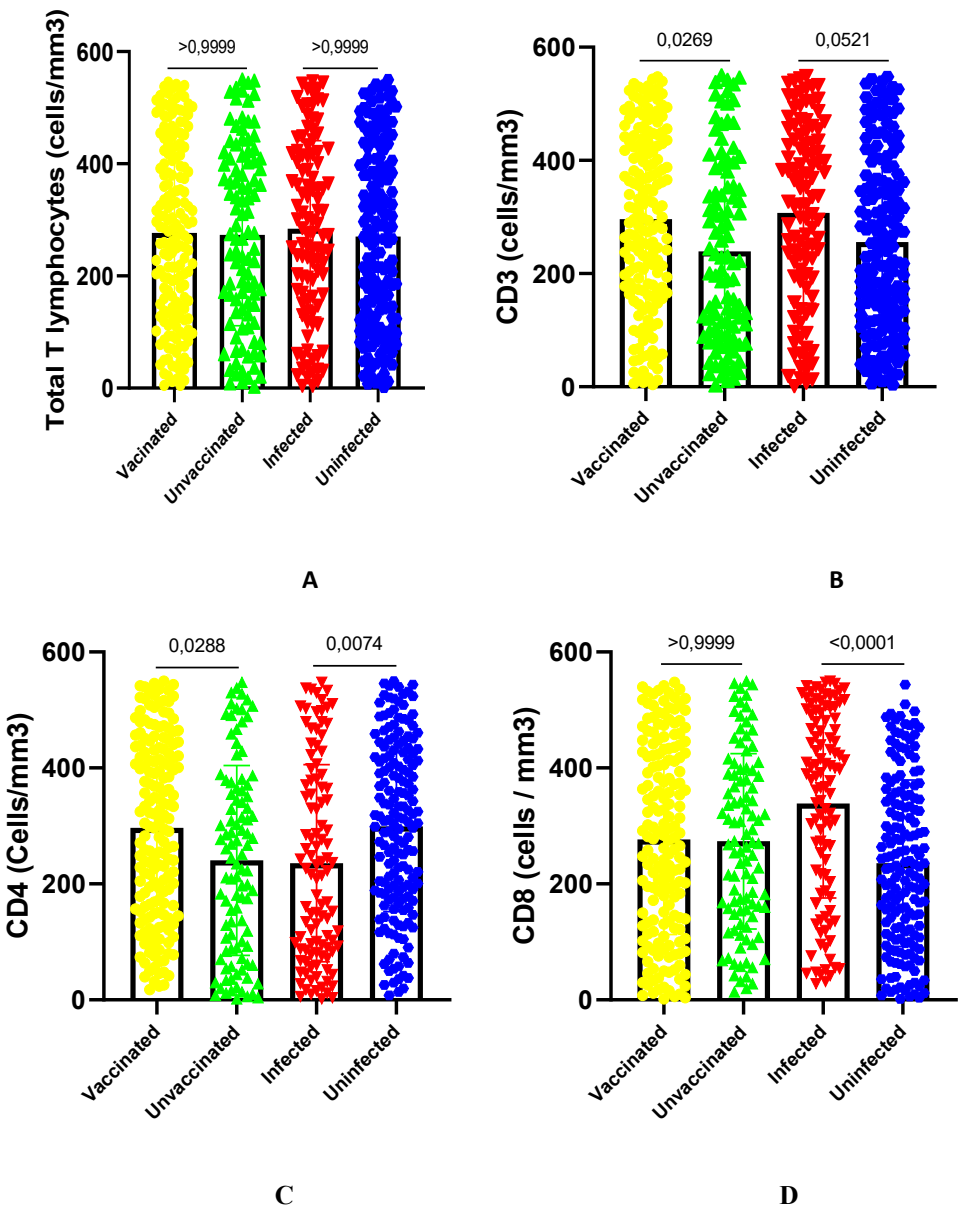


Figure 1 : Comparison of T-Cell Levels Between Vaccinated and Unvaccinated Individuals, and Between Individuals with and Without a History of Covid-19 Infection.

A : Total Lymphocytes **B** : Cd3 Lymphocytes

C : Cd4 Lymphocytes **D** : Cd8 Lymphocytes

On the other hand, according to the notion of infection, we found higher rates in those with a history of infection with a statistically significant difference ($p < 0.0001$) compared with those who had never been infected. Our observations support the hypothesis that, in patients cured of COVID-19, Th1-type responses predominate and that induction of such a response appears to be more protective [10]. Also, during natural infection, CD8+ T cells play an important role in containing infection through their ability to eliminate already infected cells [1]. Infection appears here to be a factor that confers greater (cytotoxic) CD8+ T immunity. And these cells could persist for a long time in people cured of Covid-19 [11]. What's more, some studies have shown that the majority of patients cured of this disease develop more of a CD8+ effector cell response against the virus [7].

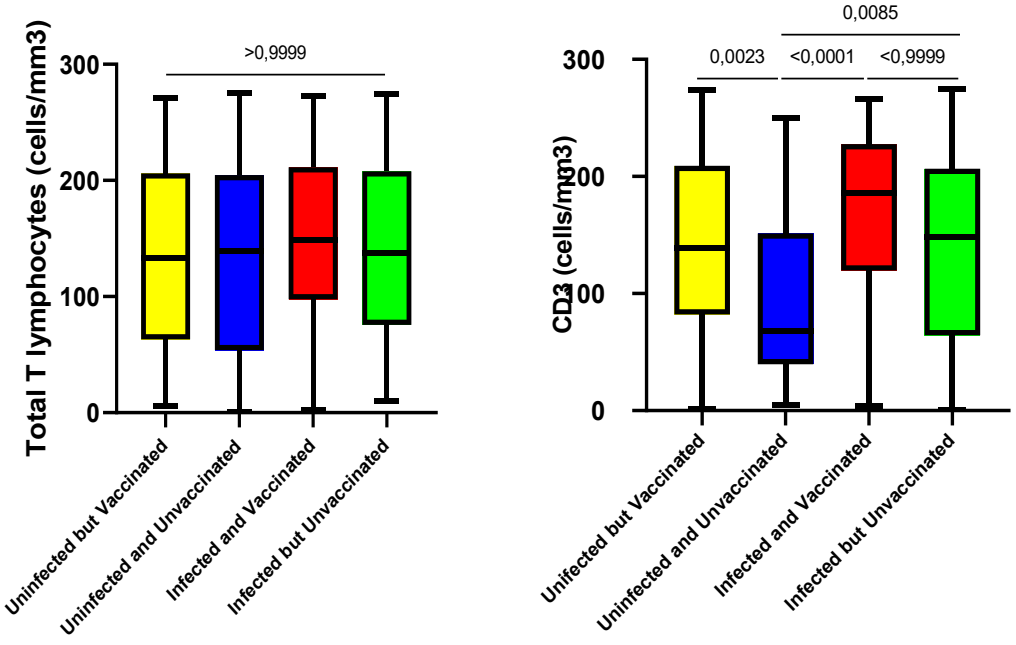
As SARS-Cov-2 is an intracellular virus, the antigenic peptides derived from its preparation by APCs will be presented directly to CD8 LTs via an MHC-I molecule, without the intervention of CD4+ LTs. This will lead to greater proliferation of CD8+ LTs.

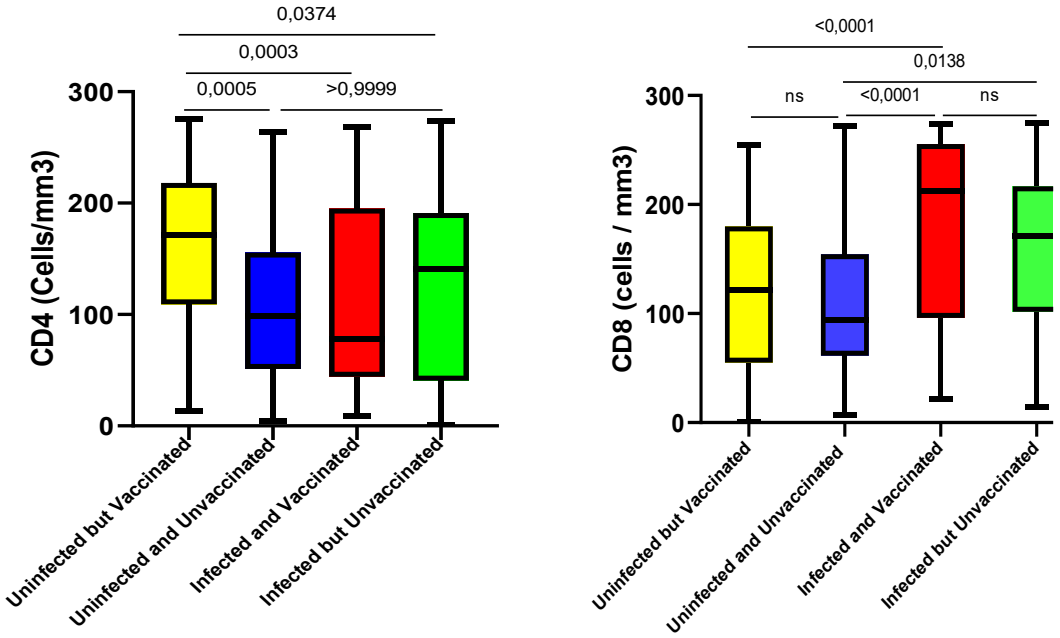
Analysis of these various findings in the different groups of our population shows that, in terms of lymphocyte levels in general, vaccination and infection have similar effects (Figure 2A). This similarity is confirmed by the study of CD3+ lymphocytes (Figure 2B). In fact, compared with subjects not exposed to any form of immunisation, the rates in vaccinated and infected subjects were higher, with significant differences. This difference was even greater when the subject had hybrid immunity ($p < 0.0001$). Vaccination and natural infection could therefore also have an effect on innate immunity, particularly on the expansion of NKT lymphocytes. However, this effect is greater in the case of vaccination. Indeed, some studies show that vaccines and the new adjuvants used in their preparation can boost adaptive immune responses by activating and proliferating NK cells including NKT cells [12,13]. But in the case of SARS-CoV-2 infection, there could be a reduction in the number of these NK cells in the peripheral blood, since this would be a technique used by the virus to escape clearance [14].

However, in terms of CD4+ LT lymphocytes, in subjects with no history of infection, the rate was statistically higher in vaccinated subjects than in non-vaccinated subjects ($p = 0.0005$) (Figure 2C). However, according to the notion of infection, whether or not there was a history of infection, there was no difference between the rates of vaccinated and non-vaccinated subjects, although the CD4+ rate was relatively lower in vaccinated subjects, which may explain the low expansion of these cells during infection. Infection therefore induces cytotoxic cellular immunity rather than regulatory immunity. We can therefore put forward the hypothesis that, when vaccination occurs in a subject with a history of infection, CD4+ clonal expansion is reduced by the combined activity of existing anti-viral antibodies and, above all, cytotoxic cellular immunity.

This hypothesis was confirmed by the higher CD4+ TL count in vaccinated patients with no history of infection (Figure 2C) compared with vaccinated patients with a history of infection, with a significant difference ($p = 0.0003$).

There was no difference in CD8+ LT between vaccinated and unvaccinated subjects with no history of Covid-19 infection (Figure 2D). However, there was a significant difference between the rates of those with hybrid immunity compared with those with artificial immunity ($p<0.0001$). Vaccination therefore appears here to be à booster of cell-mediated immunity when it occurs after an infection. Our results therefore confirm certain data in the literature which stipulate that infection prior to vaccination generates a more robust immune response [15, 16].





C **D**

Figure 2: Comparison of T-Cell Levels Between Vaccinated and Unvaccinated Individuals according to History of Covid-19 Infection

A : Total lymphocytes B : CD3 lymphocytes
C : CD4 lymphocytes D : CD8 lymphocytes

In subjects vaccinated on a history of Covid-19, the CD8+ LT rate was higher with a significant difference ($p < 0.0001$) compared to the rate in subjects not exposed to any form of immunisation.

Furthermore, in subjects who had been exposed to a natural challenge, their rate appeared higher with a significant difference ($p = 0.0138$) compared with the rate of those not exposed to any form of immunisation.

We can therefore say that, when an artificial challenge (vaccination) occurs in a field with a history of natural challenge (infection), because of the pre-existence of CD4+ TL and specific antibodies, we see a clonal contraction which will therefore limit the expansion of these CD4+ TL. Vaccination therefore has no influence on the expansion of these cells. But when this artificial challenge occurs in an area that has already been immunised following an infection, it becomes a booster for the expansion of cytotoxic cellular immunity cells, the CD8+ LT. Indeed, numerous studies in the literature indicate that prior infection already confers protection of around 80 to 95% [17, 18].

These findings at cellular level have been confirmed by studies of cytokines, sometimes with controversial results.

This study revealed that, in terms of pro-inflammatory cytokines, IL-6 levels were higher the more the subject had hybrid immunity (booster effect), with a significant difference ($p = 0.0009$). However, levels were virtually identical between a natural challenge and an artificial challenge, or even when the subject had never been exposed to any form of immunisation (Figure 3A). The same was true of the TNF study, where the rate was higher when there was a notion of coexistence of vaccination and a history of infection (Figure 3B). However, in general, the rate was lower in vaccinated subjects compared with non-vaccinated subjects ($p<0.0001$) but higher in subjects with hybrid immunity compared with those with natural challenge ($p<0.0001$).

In fact, since inflammation is a resistance mechanism, protection is all the greater if the subject has not only been infected, but also vaccinated. Vaccination alone and infection alone gave rise to the same levels of inflammatory reaction.

However, other authors have found different results, stating that there was greater production of several cytokines in cured patients than in vaccinated patients, due to the importance of other viral proteins which could also be targets for future vaccines [19].

However, we found the opposite effect for IFNγ. Levels were lower when subjects had hybrid immunity and higher when subjects were mainly vaccinated only or had only been infected (Figure 3C). Indeed, in the event of infection, there is an exacerbated release of pro-inflammatory cytokines but little production of inter-

ferons [20]. After recovery, however, IFN levels normalise or even increase. Vaccination therefore appears to be the best means of producing cytokines with antiviral activity. This finding could be justified by the fact that in the event of infection, the combined activity of anti-SRAS-CoV-2 antibodies and the direct cytotoxicity of CD8+ TL would limit the production of the latter. On the other hand, in the event of vaccination in a subject with no history of infection, these cytokines, produced not only by CD8+ LTs but also by CD4+ LTs, innate immunity cells including APCs (Monocytes/Macrophages) and, above all, plasmacytoid dendritic cells, which are cells highly specialised in antiviral immunity thanks to their production of large quantities of all type I IFNs, would lead to an increase in their levels [10].

Our results differed from those reported in numerous studies. They revealed that SARS-CoV-2-specific CD8+ LT, generated in response to infection by this virus, preponderantly (strongly) express IFNγ [7, 16,] with some expression of TNF and IL-2 [16]. This contrasts with a higher rate of CD8+ LT in vaccinees with a history of infection (Figure 2D).

These differences could be justified by the fact that in their studies, cytokine assays were performed during the course of the disease, whereas in ours, they were performed at a distance from the disease, with an average delay between infection and sampling estimated at around 11 months, with extremes of 1 month and 24 months (Table III) [21].

	Deadlines (Month)	Average	Minimum	Maximum
Types of immunisation				
Vaccination		8	1	26
Infection		11	1	24

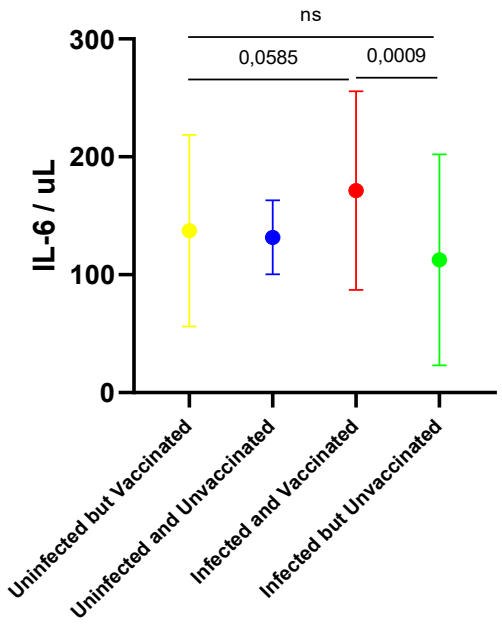
Table 3: Average Time Between Samples and Different Types of Immunisation

However, these pro-inflammatory cytokines produced by the activation of T lymphocytes, apart from their protective role, are not without consequences for the body. They can cause tissue damage if they are produced in large quantities and this production is not regulated.

We therefore compared the levels of cytokines with anti-inflammatory activity, such as IL-2 and IL-10, after vaccination with those after infection, because these limit the secretion of pro-inflammatory cytokines and thus prevent tissue damage.

The IL-2 study showed that, taken individually, vaccination and infection had approximately the same level of protection against tissue damage. However, this level of protection was higher the more the subject was vaccinated (Figure 3D). In addition to proliferating immune T cells, IL-2 acts on regulatory T lymphocytes (Treg), which in turn regulate the activity of pro-inflammatory cytokines, thereby ensuring homeostasis.

However, the findings were different for Il-10. Its level was higher when the subject was only vaccinated or only infected. On the other hand, it was lower when the subject had hybrid immunity (Figure 3E). This suggests that hybrid immunity boosts protective cellular immunity, but the deleterious effects may also be significant.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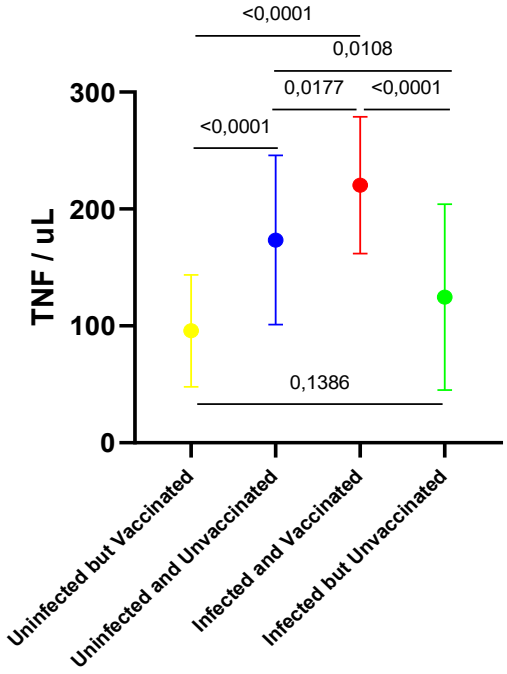
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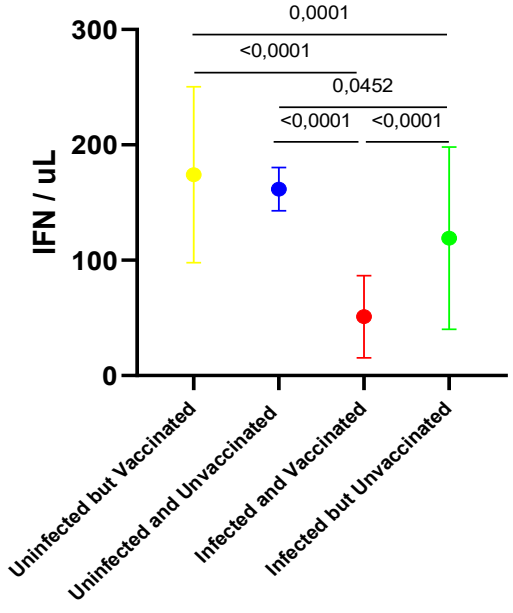
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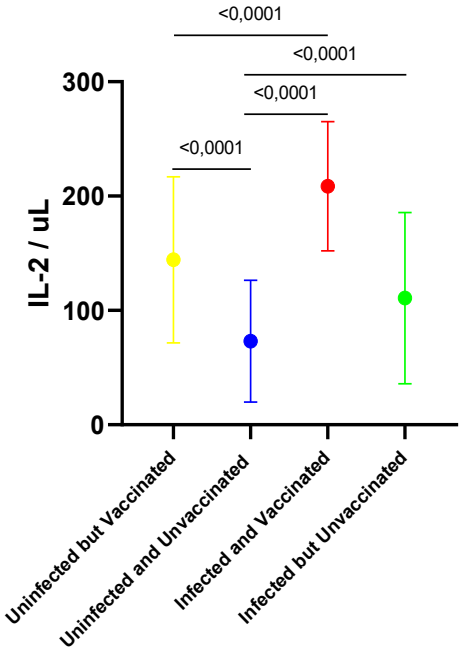
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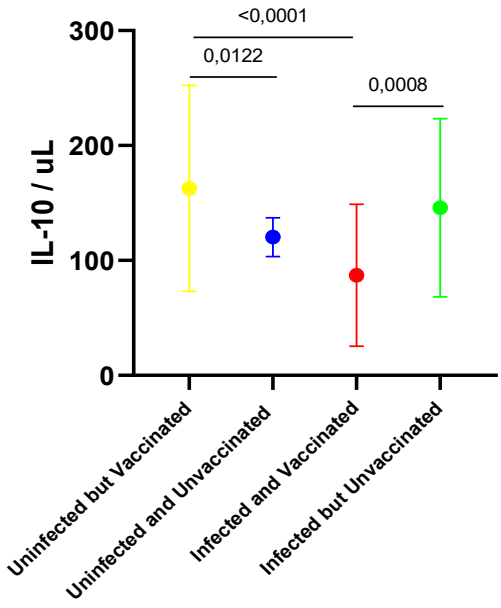

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Figure 3 : Comparison of Cytokine Levels Between Vaccinated and Unvaccinated Individuals According to History of Covid-19 Infection

A : Interleukin 6 (IL-6)

B : Tumor necrosis factor (TNF)

C : Interferon gamma (IFNɣ)

D : Interleukin 2 (IL-2)

5. Conclusion

The results of our study indicate that hybrid immunity and natural infection with SARS-CoV-2 favour a greater expansion of CD8+ cells than vaccination against Covid-19. However, during vaccination, there was greater production of CD4+ LTs, as these cells play a more important role in directing this form of immunisation towards humoral-type immunity. However, only vaccination and infection limit the occurrence of tissue damage as much as hybrid immunity, given the residual levels of pro-inflammatory cytokines.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Approval

The study was approved by the National Ethics Committee for Life and Health.

Reference number : 007-22MSHPCMU/CNESVS-km

The patients/participants provided their written informed consent to participate in this study.

The authors confirm that all the experiments were carried out in accordance with the guidelines and regulations of the Declaration of Helsinki.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are available with the corresponding author.

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Authors' Contributions

YOR, DSR and G-KAPVconceived and designed the analysis, researched data, and wrote the manuscript. YOR and AAH performed the analysis and generated the figures. AAUA, SYJ, MLRC, KHG, MS and OBD involved in sample collection, laboratory analysis and in subjects' recruitment. DSR, YOR, NK and SKL involved in the clinical design of the study and participant referrals from other hospitals. YOR, DSR and G-KAPV edited the manuscript, managed and coordinated responsibility for the research activity planning and execution. NK and SKL contributed to the discussion and Funding acquisition. All authors contributed to the article and approved the submitted version.

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