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A Comparative Study of The Effectiveness of Pfizer-BioNTech (BNT162b2), AstraZeneca (ChAdOx1nCoV-19) and Sinopharm (BBIBP-CorV) Vaccines in Eliciting Cell Mediated and Humoral Immunity in A Sample of Vaccinated Population from Iraq

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Abstract

Background Vaccine development is not an easy task but is a top priority to restore normalcy for Coronavirus-19 disease (COVID-19) and achieve the herd immunity.

Objective To compare the level and duration of humeral versus cellular immune response in vaccinated individuals at one and 8 months after second dose of three different vaccines to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), namely Pfizer, AstraZeneca, and Sinopharm vaccines.

Methods The level of neutralizing antibodies and the peripheral mononuclear cells proliferation (PBMC) activity and in vitro IFN-γ release by the S1 spike protein-stimulated T cells were monitored using isotype- and species- free competitive blocking ELISA, microculture tetrazolium assay (MTT) proliferation assay and an ELISA technique for the assessment of IFN-γ level in a cell culture supernatant, respectively.

Results PBMC proliferation percentage and the concentration of the in vitro IFN-γ release were remarkably higher in 8 months than in 1-month post-2nd dose vaccination groups of the three vaccines studied in this study (P <0.0001). For the PBMC proliferation percentage, AstraZeneca vaccine induced much higher proliferation percentage than Pfizer and Sinopharm (P <0.01), which both showed very close PBMC proliferation (P >0.05).

Conclusion AstraZeneca showed superior effect on inducing robust cellular immunity followed by Pfizer vaccine, while Sinopharm showed minimal cellular immune response induction. And for all vaccines, the cellular immunity increased with time over 8 months after vaccination. Moreover, Pfizer vaccine proved to be of highest and most durable neutralizing anti-RBD IgG antibodies and followed with Sinopharm and AstraZeneca vaccines.

Keywords COVID-19, SARS-CoV-2, RBD, vaccine, neutralizing antibodies (nABs)

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List of abbreviations: COVID-19 = Coronavirus disease 19, ELISA = Enzyme linked immunosorbent assay, PBMC = Peripheral blood mononuclear cells, PCR = Polymerase chain reaction, RBD = Receptor binding domain, SARS-CoV-2 = Severe acute respiratory syndrome-2

Introduction

Coronavirus disease-19 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2

(SARS-CoV2), has posed serious threats to public health, the global society and economy [1]. Therefore, it is imperative to develop safe and effective vaccines to defeat SARS-CoV-2 and, more importantly, the emerging variants circulating worldwide [2].

Spike(s) proteins on the surface of SARS-CoV-2 virus mainly consist of S1 and S2 domains, which are responsible for virus-cell attachment and membrane fusion, respectively, the receptor-binding domain (RBD) in the S1 subunit is the key component that directly mediate the recognition and binding of the virus to the receptor angiotensin-converting enzyme 2 (ACE2) on host cells [1,3].

The S1 and RBD are ideal targets for developing subunit vaccines against SARS-CoV-2 wild type and its variants [4,5]. However, RBD-based subunit vaccines may face some important challenges, mostly their relatively low immunogenicity, which must be combined with appropriate adjuvants, fragment lengths, and immunization schedules [6].

At Feb 3, 2021 the world has shown an impressive capacity for an accelerated COVID-19 vaccine development process, many COVID-19 vaccine candidates have been authorized or approved for human use and others were in experimental phases of clinical testing, only five of vaccines those developed by AstraZeneca in partnership with Oxford University, BioNTech in partnership with Pfizer, Gamaleya, Moderna, and Sinopharm in partnership with the Beijing Institute have been authorized by stringent regulatory agencies or WHO [7].

Among the approved vaccines, different platforms have been implemented: inactivated virus, viral vectors, and mRNA-based vaccines which focus the immune response against only the key viral proteins of interest. Generally, all of them are qualified to stimulate an immune response and are efficacious against SARS-CoV-2, even at different levels [8]. Although vaccination effectiveness against SARS-CoV-2 has been astonishing, but booster immunizations are clearly required for maintenance of effectiveness over time, they are far from perfect. Immunity wanes with time elapsed and viral antigenic variation [9].

Vaccines induce both adaptive humoral and cellular immune responses, most of the currently accepted correlates of protection are based on neutralizing antibody responses, however, if there is no detectable antibody response after vaccination the vaccines may still offer protection through cellular immunity, since cellular responses and antibody responses are often correlate to some extent [10-12].

Three vaccines were introduced to Iraq for use namely, Pfizer, AstraZeneca, and Sinopharm. These three vaccines were introduced after being tested in controlled randomized double blind clinical trials. However, none of these trials was done in Iraq. It is well known that immune response to vaccines might be affected by race, environment, age, sex, underling health conditions and level of exposure of the population to the virus [13]. Hence, it was important to set off a study investigating the cellular and neutralizing humeral immune responses in a sample of vaccinated Iraqi individuals with these vaccines and to test the longevity of the immune response of these vaccines.

The objective of the current study was to assess the humeral and cellular immune response to the currently used vaccines to COVID-19 patients.

Methods

Study design and subjects

This was a cross-sectional study of 6 groups of vaccinated volunteers who received full doses of vaccines in Baghdad province; each group consists of 30 individuals; however, at the end of the study and for technical obstacles, only 123 individuals were included. The study was conducted in the period between 15 December 2021 to 5 August 2022. The included groups were as follows: at (1 month and 8 months) post dual vaccination with Pfizer, at (1 month and 8 months) post dual vaccination with Sinopharm and at (1 month and 8 months) post dual vaccination with AstraZeneca. Accordingly, the

target of the current study was to attain a sample size of 180 individuals.

The exclusion criteria of the study population were: individuals had history of symptomatic infection, those who on immunomodulating or immunosuppressive therapy, and had any kind of immunosuppression-related disease.

The following data were taken into consideration and recorded for each participant by oral questionnaire: the name of the vaccinated healthy volunteer, age, sex, type of the vaccine received, number of the received vaccine doses, the duration after the second dose of each vaccine which was determined by the vaccination card for each individual, comorbidities such as diabetes, hypertension, cardiovascular diseases and others, negative polymerase chain reaction (PCR) result if done so far, absence of COVID-19 signs and symptoms, and not being in contact with an infected individual, to assure healthy status, and having an immunosuppressive disease or taking immune-suppressive or modulating drugs.

These data were adjusted to the selection criteria at the time of sample collection, the volunteers were selected from Baghdad with the help of Al-Kadhimiya vaccination regional center.

Ethical approval

The study was approved by the Institutional Review Board at al Nahrain University, College of Medicine under number 20211047 on 12/11/2021. Informed consent was obtained from all subjects to participate in the study.

Limitation of the study

The limitations of the current study were: discontinuity of vaccine supply precisely AstraZeneca vaccine, vaccine reluctance and vaccination hesitancy, the highest transmissibility Omicron variant outbreak, third vaccine dose recommendation, heterologous prime-boost vaccination and uncertainty of healthy status and possibility of asymptomatic COVID-19 infection.

Samples collection

Up to 3 ml of non-anticoagulant whole blood were drawn into 10 ml serum separator tubes for serum isolation to determine the amount and level of anti RBD-Neutralizing antibodies by indirect competitive inhibitory enzyme linked immunosorbent assay (ELISA) kit. The blood was allowed to clot at room temperature for about two hr. Then, it was centrifuged for 10 min at 1000 g and the resultant serum was isolated and stored at C at -20°C in aliquots for later use in ELISA.

The remaining 2 ml of blood were drawn into ready-made sodium citrate containing tube to isolate peripheral blood mononuclear cells (PBMC) in order to evaluate the immunological reactivity of PBMC of vaccinated healthy volunteers in response to viral spike protein as a stimulator (since S1 contains major immunodominant epitopes) to measure the duration of cell activation and proliferation using the methyl microculture tetrazolium (MTT) assay.

Up to 60 µl of cell culture supernatant were collected at the second day of stimulation (at 24 hr incubation period) for the measurement of interferon gamma (IFN-γ) level secreted by activated cells using human interferon gamma ELISA kit.

Microculture MTT

After preparation of PBMC-complete Roswell Park Memorial Institute (RPMI) 1640 media suspension, approximately (13×10^4) cells in 135 µl complete RPMI 1640 media were plated as following: one tube with recombinant SARS-CoV-2 S1 protein, positive control and one tube without SARS-CoV-2 protein for negative control.

PBMC-RPMI 1640 media with/without S1 protein were plated for each individual, and read by ELISA reader at 490 nm at the end [14].

Recombinant SARS-CoV-2 protein was diluted by phosphate-buffered saline (PBS) to concentration 10 µg/ml and stored at -20°C in aliquots to minimize freezing thawing cycles. Up to 15 µl of recombinant SARS-CoV-2 protein was

added into each tube to be 1 µg/ml, the stimulatory concentration used [15]. It is noteworthy to mention that S1 protein concentration was achieved according to other researches to measure the proliferation of PBMC [16-18]. At 24 hr of incubation, positive and negative control tubes were centrifuged for 5 min at 200 g to collect cell culture supernatant in to aseptic tubes to be used for the measurement of IFN-γ level.

ELISA kit to assess human IFN-γ levels

This ELISA kit used is a Sandwich-ELISA. The micro-ELISA strip plate provided in this kit (Sunlong biotech, China. Ref. SL0960Hu) has been pre-coated with an antibody specific to IFN-γ. Standards or samples were added to the appropriate micro-ELISA strip plate wells and combined to the specific antibody. Then a horseradish peroxidase (HRP)-conjugated antibody specific for IFN-γ was added to each micro-ELISA strip plate well and incubated. Free components were washed away. The 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution was added to each well. Only those wells that contain IFN-γ and HRP conjugated IFN-γ antibody appeared blue in color and then turned yellow after the addition of the stop solution. The optical density (OD) was measured spectrophotometrically at a wavelength of 450 nm. The OD value is proportional to the concentration of IFN-γ.

Isotype-free competitive ELISA for the detection and quantification of SARS-COV-2 neutralizing antibodies in the serum of vaccinated healthy individuals.

This ELISA kit uses competitive-ELISA as the method to quantitatively detect and quantify anti-SARS-CoV-2 neutralization antibodies in the serum. The micro-ELISA plate provided in this kit (SARS-CoV-2 Neutralization Antibody ELISA Kit. Elabscience, USA. Cat No.: E-EL-E608) is pre-coated with recombinant human ACE2. During the reaction, the SARS-CoV-2 neutralization antibodies in the pretreated samples or controls competes with a fixed amount of human ACE2 on the solid phase supporter for sites on the HRP conjugated recombinant SARS-CoV-2 RBD fragment (HRP-RBD). After incubation at 37℃, the unbound HRP-RBD as well as any HRP-RBD bound to non-neutralization antibody were captured on the plate and eventually form the ACE2-RBD-HRP complex, while the circulating neutralization antibodies HRP-RBD complexes remain in the supernatant and were removed during washing. Then a TMB substrate solution was added to each well. The enzyme-substrate reaction is terminated by the addition of stop solution and the color change was measured spectrophotometrically at a wavelength of 450±2 nm. The inhibition ratio resulted indicated the level of SARS-CoV-2 neutralization antibodies exists in the tested samples. The concentration of SARS CoV-2 neutralization antibodies in the samples was then determined by comparing the OD of the samples to the OD of the kit standard curve.

Statistical analysis

The data were analyzed to parametric and non-parametric and student t-test and ANOVA were used for quantitative data while Chi-square test was used for qualitative data. P values <0.05 were considered significant.

Results

Characteristics of the participants in the study

To compare the effectiveness of the elicited humoral and cellular immune responses from the used COVID-19 vaccines in Iraq namely: Pfizer, AstraZeneca and Sinopharm,123 healthy supposedly non-infected vaccinated volunteers were assessed and classified into mainly 6 groups; each group was subdivided into two groups according to the vaccine type, duration of post 2nd vaccine dose and age.

Up to 50 individuals (40.7%) were vaccinated with Pfizer, 35 (28.5%) were vaccinated with AstraZeneca and 38 (30.9%) were vaccinated with Sinopharm and 47 individuals (38.2%) were at 1 month duration post 2nd dose of vaccination

and 76 (61.8%) were at 8 months duration post 2nd dose.

Groups of the vaccinated individuals

A total of 22 vaccinated individuals (17.9%) were at 1 month duration post vaccination with the 2nd dose of Pfizer vaccine and 28 vaccinated individuals (22.8%) were at 8 months.

A total of 8 vaccinated individuals (6.5%) were at 1 month post vaccination with the 2nd dose of AstraZeneca and 27 vaccinated individuals (22%) were at 8 months post vaccination.

A total of 17 vaccinated individuals (13.8%) were at 1month post vaccination with the 2nd dose of Sinopharm vaccine and a total of 21 vaccinated individuals (17.1%) were at 8months post vaccination.

Vaccine induced cellular and humoral immunity against SARS -COV-2 considering vaccine type

In regard to the PBMC proliferation percentage, it was revealed that the participants of AstraZeneca vaccine showed much higher proliferation percentage than participants of Pfizer and Sinopharm ($P < 0.01$) and both Pfizer and Sinopharm participants showed very close percentages of PBMC proliferation ($P > 0.05$). For the concentration of the in vitro IFN-y release, again AstraZeneca group revealed distinguishing higher levels than Sinopharm and Pfizer groups ($P < 0.0001$); nevertheless, unlike the trend found with the PBMC proliferation %, Pfizer group showed significantly higher concentration of the in vitro lFN-y release than Sinopharm group ($P < 0.05$). In regard to the serum level of the neutralizing IgG antibodies, Pfizer group revealed the highest level compared to AstraZeneca and Sinopharm groups ($P < 0.05$); the Sinopharm showed trend of higher levels of neutralizing antibodies than AstraZeneca but without reaching statistical significance ($P > 0.05$) as shown in table (1).

Table 1. Comparison among Pfizer, AstraZeneca and Sinopharm vaccines in PBMC proliferation, neutralizing antibodies and in vitro concentration of IFN-γ

Parameters	Vaccine type	No.	Mean Rank	Median	P value*
Proliferation percentage	Pfizer	50	57.53	18.2	0.006
	AstraZeneca	35	77.79	76	
	Sinopharm	38	53.34	29	
	Total	123			
nAb** concentration (µg/ml)	Pfizer	50	72.83	4.3	0.019
	AstraZeneca	35	54.97	3.7	
	Sinopharm	38	54.22	3.95	
	Total	123			
IFN-γ concentration (pg/ml)	Pfizer	50	61.20	100.8	<0.0001
	AstraZeneca	35	94.26	174	
	Sinopharm	38	33.34	40.3	
	Total	123			

*: Kruskal-Wallis test, **: nAb= neutralizing antibodies

Vaccine induced cellular and humoral immunity against SARS- COV-2 considering the study groups

By using Kruskal Wallis test, the proliferation percentage was shown to be significantly different among the study groups (P <0.01); for 1-month participants, marginally Sinopharm was highest, then AstraZeneca, and lowest value in Pfizer group; for 8-month participants, AstraZeneca was far highest (P <0.01), then Pfizer then Sinopharm. These findings unravel that AstraZeneca vaccine especially at 8 months' time interval post vaccination was the most effective in stimulating lymphocytes proliferation when compared to the other two vaccines.

For IgG anti-RBD neutralizing antibodies concentration µg/ml in 1 month and 8 months post vaccination, it was shown that the median levels were significantly different among the study groups (P <0.01). It was found that Pfizer then AstraZeneca, then Sinopharm induced the highest median levels of neutralizing antibodies 1 month post vaccination, respectively (P <0.05); on contrary, for 8 months post vaccination, Sinopharm, then, Pfizer, and AstraZeneca induced highest levels of neutralizing antibodies, respectively, (P <0.05). Altogether, the current findings reveal that Pfizer vaccine, then AstraZeneca, then Sinopharm are the best ones for inducing high neutralizing antibodies shortly after the vaccination; nevertheless, AstraZeneca proved to be short in preserving good level of neutralizing antibodies after 8 months of vaccination while the best vaccine found to preserve highest levels of neutralizing antibodies 8 months after vaccination was Sinopharm then Pfizer.

For the in vitro Interferon-γ release, it was found that levels are highly variable among the study groups (P <0.0001). For both 1-month and 8-months groups, the far highest levels of IFN-γ release seen in AstraZeneca, then in Pfizer and then in Sinopharm (P <0.01). Accordingly, both AstraZeneca and Pfizer vaccines were found to be highly successful in inducing IFN-γ synthesis and release which is a necessary step for T-

helper 1 polarization and specific cellular immunity stimulation, while, on contrary, Sinopharm vaccine proved to be relatively poor in inducing IFN-y synthesis and release which in turn becomes short in stimulating the specific cellular immunity to SARS-CoV-2, as clarified in table (2).

Table 2. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in Pfizer (1 and 8 months) versus AstraZeneca (1 and 8months) versus Sinopharm (1and 8 months)

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Pfizer 1 month post vaccination	22	52.18	9	0.006
	Pfizer 8 months post vaccination	28	61.73	33.3	
	AstraZeneca 1 month post vaccination	8	52.69	18.2	
	AstraZeneca 8 months post vaccination	27	85.22	89	
	Sinopharm 1 month post vaccination	17	54.03	30	
	Sinopharm 8 months post vaccination	21	52.79	28.6	
	Total	123			
nAb concentration (µg/ml)	Pfizer 1 month post vaccination	22	95.36	4.4	<0.001
	Pfizer 8 months post vaccination	28	55.12	3.6	
	AstraZeneca 1 month post vaccination	8	82.69	4.3	
	AstraZeneca 8 months post vaccination	27	46.76	3.4	
	Sinopharm 1 month post vaccination	17	59.29	4	
	Sinopharm 8 months post vaccination	21	50.12	3.7	
	Total	123			
IFN-y concentration (pg/ml)	Pfizer 1 month post vaccination	22	37.07	53.8	<0.0001
	Pfizer 8 months post vaccination	28	80.16	140.4	
	AstraZeneca 1 month post vaccination	8	63.12	102.2	
	AstraZeneca 8 months post vaccination	27	103.48	197.2	
	Sinopharm 1 month post vaccination	17	17.03	31.6	
	Sinopharm 8 months post vaccination	21	46.55	51.4	
	Total	123			

*: Kruskal Wallis test

Vaccine induced cellular and humoral immunity comparison among different vaccine and between different time interval

Comparison of cellular and humoral immunity between 1 month of Pfizer vaccination and 1 month of AstraZeneca vaccination

PBMC proliferation percentage at 1 month of vaccination for Pfizer and AstraZeneca showed close effect to each other (P >0.05); however, AstraZeneca showed a better trend in stimulating PBMC proliferation 1 month after vaccination. For neutralizing antibodies stimulation 1 month after vaccination, both vaccines performed very similarly (P >0.05) with marginal higher levels of antibodies by Pfizer than AstraZeneca. However, for the level of the in vitro IFN-y release the story is different. AstraZeneca vaccine effectively induced the synthesis and release of IFN-y by PBMC much better than Pfizer did just 1 month after the second dose of vaccination (P <0.01), as shown in table (3).

Table 3. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in Pfizer and AstraZeneca both at 1 month post 2nd dose

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Pfizer 1 month post vaccination	22	15.23	9	0.8
	AstraZeneca 1 month post vaccination	8	16.25	18.2	
	Total	30			
nAb concentration (µg/ml)	Pfizer 1 month post vaccination	22	16.30	4.4	0.42
	AstraZeneca 1 month post vaccination	8	13.31	4.3	
	Total	30			
IFN-y concentration (pg/ml)	Pfizer 1 month post vaccination	22	12.57	53.8	0.001
	AstraZeneca 1 month post vaccination	8	23.56	102.2	
	Total	30			

*: Mann-Whitney test

Comparison of cellular and humoral immunity between 8 months of Pfizer vaccination and 8 months of AstraZeneca vaccination

In regard to the cellular immunity indices, namely proliferation percentage and in vitro IFN-y release at 8 months post Pfizer and post AstraZeneca vaccinations, the findings were clear for showing the superiority of AstraZeneca vaccine over Pfizer vaccine (P <0.05). More to the point, AstraZeneca was excellent in inducing IFN-y release compared to Pfizer and the difference was highly significant (P <0.0001), as illustrated in table (4). Hence, AstraZeneca vaccine proved to be the best choice for preserving highest cellular immunity for the longest period when compared to Pfizer vaccine.

Table 4. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in Pfizer and AstraZeneca vaccines both at 8months of 2nd vaccine dose

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Pfizer 8 months post vaccination	28	23.11	33.3	0.021
	AstraZeneca 8 months post vaccination	27	33.07	89	
	Total	55			
nAb concentration (µg/ml)	Pfizer 8 months post vaccination	28	29.41	3.6	0.5
	AstraZeneca 8 months post vaccination	27	26.54	3.4	
	Total	55			
IFN-y concentration (pg/ml)	Pfizer 8 months post vaccination	28	18.70	140.4	<0.0001
	AstraZeneca 8 months post vaccination	27	37.65	197.2	
	Total	55			

*: Mann-Whitney test

Comparison of cellular and humoral immunity between Pfizer and Sinopharm vaccination both at 1month post vaccination

At 1 month post Pfizer vaccination and 1month post Sinopharm vaccination, (P >0.05), Pfizer vaccine performed much better than Sinopharm in inducing neutralizing antibodies and stimulating IFN-y release just 1 month after the vaccination (P <0.05) as shown in table (5).

Table 5. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in Pfizer and Sinopharm vaccines both at 1 month

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Pfizer 1 month post vaccination	22	19.66	9	0.83
	Sinopharm 1 month post vaccination	17	20.44	30	
	Total	39			
nAb concentration (µg/ml)	Pfizer 1 month post vaccination	22	26.14	4.4	<0.001
	Sinopharm 1 month post vaccination	17	12.06	4	
	Total	39			
IFN-y concentration (pg/ml)	Pfizer 1 month post vaccination	22	24.80	53.8	0.002
	Sinopharm 1 month post vaccination	17	13.79	31.6	
	Total	39			

*: Mann-Whitney test

Comparison of cellular and humoral immunity between Pfizer and Sinopharm vaccination both at 8month post vaccination

At 8 months post Pfizer and Sinopharm 2nd dose, both PBMC proliferation percentage and level of neutralizing antibodies were in close values (P >0.05). Unlike 1-month post vaccination, the serum level of neutralizing antibodies 8 months after vaccination with Sinopharm became close to that of Pfizer or in other words the level of neutralizing antibodies in Sinopharm group did not fall as much as that of Pfizer 8 months after vaccination indicating that although neutralizing antibodies triggered by Sinopharm was initially lower than that by Pfizer vaccine, the level of neutralizing antibodies in Sinopharm group persisted better for 8 months than in Pfizer group. For the in vitro release of IFN-y, Pfizer vaccine stimulated IFN-y far higher than Sinopharm vaccine after 8 months of vaccination (P <0.0001). Unlike Pfizer, this confirms the poor performance of Sinopharm in inducing and maintain cellular immunity to SARS-CoV-2 as shown in table (6).

Table 6. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in Pfizer and Sinopharm vaccines both at 8 months

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Pfizer 8 months post vaccination	28	26.30	33.3	0.45
	Sinopharm 8 months post vaccination	21	23.26	28.6	
	Total	49			
nAb concentration (µg/ml)	Pfizer 8 months post vaccination	28	26.18	3.6	0.5
	Sinopharm 8 months post vaccination	21	23.43	3.7	
	Total	49			
IFN-y concentration (pg/ml)	Pfizer 8 months post vaccination	28	32.05	140.4	<0.0001
	Sinopharm 8 months post vaccination	21	15.60	51.4	
	Total	49			

*: Mann-Whitney test

Comparison of cellular and humoral immunity between AstraZeneca and Sinopharm vaccines both at 1month post vaccination

Except for the PBMC proliferation percentage, the level of neutralizing antibodies and the IFN-y in vitro release was much higher in participants of AstraZeneca than in Sinopharm vaccines 1 month after the second dose (P <0.05) as clarified in table (7).

Table 7. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in AstraZeneca and Sinopharm vaccines both at 1month post 2nd dose

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Astrazeneca 1 month post vaccination	8	13.19	18.2	0.93
	Sinopharm 1 month post vaccination	17	12.91	30	
	Total	25			
nAb concentration (µg/ml)	Astrazeneca 1 month post vaccination	8	17.56	4.3	0.031
	Sinopharm 1 month post vaccination	17	10.85	4	
	Total	25			
IFN-y concentration (pg/ml)	Astrazeneca 1 month post vaccination	8	21.25	102.2	<0.0001
	Sinopharm 1 month post vaccination	17	9.12	31.6	
	Total	25			

*: Mann-Whitney test

Comparison of cellular and humoral immunity between AstraZeneca and Sinopharm vaccination both at 8months post vaccination

Although AstraZeneca induced neutralizing antibodies better than Sinopharm early (1 month after vaccination), the remaining level of neutralizing antibodies after 8 months in both vaccines was very close to each other (P >0.05) indicating a similar long-term efficacy in persisting humeral immunity. Unlike 1 month post vaccination when both AstraZeneca and Sinopharm induced PBMC proliferation very similarly, after 8 months of vaccination AstraZeneca induced PBMC proliferation far better than Sinopharm did (P<0.05) indicating a slow and persistent increase in stimulation of PBMC response to SARS-CoV-2 spike antigen presented by AstraZeneca vaccine but not by Sinopharm vaccine. For the in vitro IFN-y release, like in 1month post vaccination, AstraZeneca showed far superior effect than that of Sinopharm (P<0.05) as clarified in table (8).

Figure 8. The mean rank and median values along with the P values of proliferation percentages of PBMC, concentration of neutralizing antibodies, and in vitro concentration of IFN-y in AstraZeneca and Sinopharm both at 8 months post vaccination

Parameters	Study group	No.	Mean Rank	Median	P value*
Proliferation percentage	Astrazeneca 8 months post vaccination	27	30.81	89	<0.0001
	Sinopharm 8 months post vaccination	21	16.38	28.6	
	Total	48			
nAb concentration (µg/ml)	Astrazeneca 8 months post vaccination	27	24.09	3.4	0.82
	Sinopharm 8 months post vaccination	21	25.02	3.7	
	Total	48			
IFN-y concentration (pg/ml)	Astrazeneca 8 months post vaccination	27	32.96	197.2	<0.0001
	Sinopharm 8 months post vaccination	21	13.62	51.4	
	Total	48			

*: Mann-Whitney test

Correlations among proliferation percentage, levels of neutralizing antibodies and INF-y in vitro release in the population of the study

The correlational behavior among quantitative variables of proliferation percentage and levels of neutralizing antibodies and INF-y in vitro release in 123 individuals participated in this study was calculated in terms of Spearman's correlation coefficient, or r, along with the significance P value of each correlation. It was found that the PBMC proliferation percentage was 24.5% positively correlated with the level of in vitro IFN-y release (P <0.05) while the neutralizing antibodies level was shown to be 23.4% inversely correlated with the level of IFN-y in vitro release (P<0.05) as shown in table (9).

Table 9. Correlation coefficient, r, along with the corresponding significance P values among age, proliferation percentage, levels of neutralizing antibodies and INF-y in vitro release in 123 study participants

Parameters		Age (yr)	Proliferation percentage	nAb concentration (µg/ml)
Proliferation percentage	r	0.045		
	P	0.619		
nAb concentration (µg/ml)	r	0.163	-0.010	
	P	0.071	0.911	
IFN-y concentration (pg/ml)	r	0.029	0.245**	-0.234**
	P	0.746	0.006	0.009

**: Correlation is significant at the 0.01 level (2-tailed)

Regression of the independent INF-y concentration versus the dependent neutralizing antibodies level and the dependent proliferation percentage

Assuming IFN-y synthesis and release is the governing factor for T-helper cells behavior and polarization, hence IFN-y level was considered as independent factor in the regression analysis versus proliferation of PBMC and level of neutralizing antibodies as dependent factors. There was a significant negative correlation and linear regression of neutralizing antibodies level dependent on concentration of IFN-y concentrations (P <0.05). Moreover, there was a significant positive correlation and linear regression of PBMC proliferation percentage as dependent factor on the concentration of IFN-y concentrations (P <0.05) as shown in tables (10 and 11).

Table 10. Regression of IgG neutralizing antibodies level upon INF-y release

Parameters		nAb concentration (µg/ml)
IFN-y concentration (pg/ml)	r	-0.234
	P	0.03

Table 11. Regression of proliferation percentage upon INF-y release

Parameters		Proliferation percentage
IFN-y concentration (pg/ml)	r	0.245
	P	0.002

Discussion

The current study kept up with many other studies, conducted across the world, not only to subdue the continuing pandemic but to compare the effectiveness of the approved and rolled out vaccines as well; the matter helps to figure out the vaccine with the best effectiveness for COVID-19 and for future emerging virus variants.

Our findings revealed that all studied vaccines namely, Pfizer, AstraZeneca, and Sinopharm, yielded significantly higher neutralizing humoral immunity 1 month than in 8 months' time interval after 2-doses vaccination; whereas, on contrary, cellular immunity was found to steadily increase after 2-doses vaccination as the level of SARS-CoV-2 specific cellular immunity was found to be remarkably higher in 8 months than in 1 month interval after the second dose of vaccines.

Nonetheless, considering vaccine types, Pfizer, AstraZeneca and Sinopharm, Pfizer vaccine showed to be significantly of the highest neutralizing effectiveness especially at 1 month post 2nd vaccination while AstraZeneca showed to be significantly of the highest cellular immunity especially at 8 months rendering the other two studied vaccines with lower cellular effectiveness. As such, cellular and neutralizing humoral immunity were shown to be significantly different among the study groups.

Seemingly, when nAbs blocked the certain epitopes of S1 unit of SARS-CoV2 spike, B-cells stopped to proliferate while the T-cells continued to be stimulated due to the unblocked epitopes then differentiated into effector and memory subsets, as such nAbs declined with time elapsed while cellular responses exceled by 8 months. An interplay between the elicited humoral and cellular immune responses [19].

An association of vaccine-induced immunity with vaccine types and vaccine platforms, the cytoplasmic localization of the mRNA-encoded proteins allows for direct intracellular processing of the translated S proteins, thereby efficiently presenting peptide fragments in major histocompatibility complex (MHC)-I complexes to CD8+ T cells. Finally, exposure of S proteins in the extracellular environment makes them accessible for MHC-II antigen processing by bystander cells on the translated proteins can contribute to the antigen presentation to CD4+ T- helper cells [19]. Hence, Pfizer vaccine elicit n Abs more efficiently than AstraZeneca and Sinopharm did; attributed to the novel platform design of this vaccine which help translate mRNA of RBD domain in a robust and quick manner [20]. Anyway, AstraZeneca and Sinopharm performed similarly well in eliciting nAbs and they generated quite enough level of nAbs.

Uniquely, a potential advantage of inactivated vaccines over other vaccine types is that they comprise all viral structural proteins which may induce a broader spectrum of immunity in addition to nAbs against RBD, this means that more epitopes, especially those conserved epitopes in proteins other than spike engaged, typically elicit broad and potent humoral and cellular immune responses [21,22].

A replication-deficient modified simian adenovirus ChAdOx1 carries the transgene of the SARS-CoV-2 spike protein into the nucleus, where it is transcribed into mRNA by DNA polymerase which will be then translated and presented as a real viral infection within MHC-class I [23,24]; in agreement of the current study with a study by Swanson et al [25], individuals who got the ChAdOx1 nCoV-19 vaccine had significantly increased IFN-γ and IL-2 level beside rapidly proliferated T cells with spike protein specific T helper 1 cell bias.

The three vaccines tested in the current study behaved in some aspects quite differently and in other aspects behaved similarly. All the vaccines tested revealed a clear decline in the humeral immunity over 8 months post-vaccination. This is in harmony with previous studies [26-28]. This is explained by the fact that Coronaviridae family have the tendency to induce short-to midterm memory B cells and SARS-CoV-2 is not an exception. As known, humeral immunity is the only arm of immunity is considered a protective immunity [29-31]. Hence, all the tested vaccines provide up to 6-12 months protection only.

In fact, Pfizer and AstraZeneca elicited nAbs at quite close levels in both 1- and 8-months interval while Sinopharm lagged behind in

eliciting nAbs in 1 month interval when compared to Pfizer and AstraZeneca; however, Sinopharm compensated that shortage at 8-month interval where nAbs level of Sinopharm became comparable to that of Pfizer and AstraZeneca. This indicated several notions: First, Pfizer and AstraZeneca vaccine are potently inducing humeral immunity weeks after the second dose while Sinopharm lags behind in this completion indicating long-time production process. Second, the rate of decline of nAbs level by Sinopharm was shown to be significantly slower than Pfizer and Astrazeneca vaccines. This might be explained that inactivated whole viruses are slow triggers of humoral immunity when compared to other designs and platforms but being whole virus with multiple antigens might makes vaccine of more durable trigger. This was seen as well by other studies [32-34], while other studies contradicted this observation [35-37].

The cellular immunity was measured in this study by two factors: the proliferation percentage of lymphocytes and the release of IFN-y. The proliferation percentage represents the aptitude of lymphocytes to proliferate for clonal expansion while IFN-y is tailored to the downstream T-lymphocytes polarization to Th1 and cellular cytotoxicity, which is the cornerstone of cellular antiviral immunity. Interestingly, all vaccines studied in the current study showed significant increase in the proliferation percentage of PBMC and in vitro release of IFN-y over 8 months post vaccination. This observation attracts careful speculation as it is quite known that cellular immunity of Coronaviruses does not fade easily and persist for maybe decades; however, in this study it is found out that SARS-CoV-2 cellular immunity increases overtime after vaccination. Some studies contradict this observation [38-40] and some support it [41-45]; anyway, for the tested Iraqi vaccinated people, this trend seemed obvious. The explanation of this consistently increase in the indices of cellular immunity after vaccination might be due to continuous exposure of Iraqi individuals to the virus with asymptomatic or mild-moderate symptomatic infection which in turn would augment the cellular immunity. However, a question might be laid then why the humeral immunity is not augmented as well? The answer might be because of the emergence of variants of concern that show some level of changes in epitopes recognized by nAbs but not quite same variations in the epitopes recognized by cellular immunity. It is well known in the field that epitopes of cellular immunity are almost always more conserved than epitopes recognized by humoral arm of immunity [46]. By all means, increasing level of cellular immunity in the sample of vaccinated people of the current study is a positive sign of vaccination success which affects mainly the subsequent severity of infection rather than protection against infection. In fact, sterilizing immunity is a rare outcome of viral vaccines [47].

Almost all studies have focused on the magnitude of the spike-specific antibody response or neutralizing titer. In contrast, much less attention has been given to the magnitude or functional profile of cellular immune responses. AstraZeneca was shown to be the golden horse in terms of inducing vigorous and quick cellular immunity and followed with Pfizer while Sinopharm performed least. It is obviously an expected result. A study by Moss [48] concluded that the magnitude of spike-specific T cell induction varies according to vaccine subtype, with the adenovirus-based platforms generating stronger responses while mRNA platforms develop higher antibody titers. This has led to interest in the use of heterologous vaccine platforms. Inactivated whole virus vaccines are known to be weak inducers for cellular immunity as the killed virus is kept outside cells and thus no role of MHC-class I and II are actively involved which results in only shallow level of induction of cellular immunity relied mainly on the phagocytosed fragments of the whole killed virus antigens. On the other hand, mRNA and viral vector vaccines are designed to exploit the cellular machinery for viral antigen transcription and translation, the process mimics the natural viral infection. Hence, MHC class I and II- mediated presentation of viral antigens will be engaged and this would ensure a potent TCR-mediated signaling of T cells clonal expansion and polarization [49]. Therefore, it is evident that

Sinopharm has no chance to keep pace with the other two vaccines in inducing the same level of cellular immunity. This observation is backed by several studies [50-52].

More deeply to the context, a question might be pondered that why AstraZeneca vaccine performed much better than Pfizer vaccine in inducing both clonal expansion of PBMC and T helper (Th)1 polarization. There might be no straight forward answer; however, speculatively, the proliferation-deficient viral vectors – based vaccines seem to mimic the natural viral infection more closely than mRNA-based platforms; moreover, the viral vector itself might play a role in augmenting cellular immune response by adjuvant-like manner [53]. Nevertheless, mRNA-based vaccines are advantageous over viral vector vaccines in repeatability and easiness of production and tailoring for variants of concern [22]. Moreover, comparatively, AstraZeneca, employed full length spike glycoprotein without mutations, whereas, Pfizer contains the coding sequence of a full-length S with two proline substitutions [54], this might be the causes of this different rate of cellular response, which needs more elaborative studies.

Another observation from the current study is that Sinopharm vaccine relatively did well in inducing the proliferation percentage of PBMC and the level was a bit comparable to that of other two vaccines but the pitfall was that Sinopharm vaccine exerted poorly in inducing IFN-y synthesis. In another words Sinopharm vaccine did not succeed in stimulating T lymphocyte polarization to Th1 cytotoxic profile, which is a milestone for the progression of the antiviral cytotoxicity. In this endeavor, monitoring in vitro release of IFN-y helped in differentiating real world portfolio of cell-mediated response to the studied vaccines. Accordingly, measuring solely the proliferation percentage of PBMC is not enough for comparatively studying vaccines response as PBMC proliferation percentage is merely the first step of a long cascade of antiviral cellular immune response [55].

Actually, in regard to variant prone virus vaccines with potent cell-mediated immune response are referred over those with poor responses. T-cell response can fight better with SARS-CoV-2 new variants due to the variation of the HLA-specific T-cell epitopes among individuals and their wide distribution across proteins; thus, escaping from T-cell response is much harder [56].

According to our findings we can suggest that AstraZeneca vaccine is the most potent stimulator for the release of INF-y, which means AstraZeneca is the best vaccine for cell mediated immunity triggering and T cell polarization, while Pfizer was with the best elicited humoral neutralizing immunity.

Taken together, Pfizer and AstraZeneca groups both at 8months post 2-doses vaccination, the assessment of the performance of the two vaccines revealed almost close sustained levels of neutralizing humoral immunity by month 8, with a massive diversity in elicited cellular immunity in the long term in favor of AstraZeneca group. And we observed that better sustained levels of neutralizing response at month8 might be elicited in Sinopharm group than in Pfizer, and greater cellular response was in favor of Pfizer group by 8 months.

The findings of the current study revealed that in vitro release of IFN-y is positively correlated with the proliferative percentage of PBMC and negatively correlated with the level of nAbs. This is explained by the central downstream role of IFN-y inTh1 polarization which in turn has positive feedback on the rate of T cells proliferation and suppressant effect on the Th2 line, which is mainly involved in the humoral neutralizing immunity [57]. This is found in other previous studies [58-60]. However, does it necessarily mean the good vaccine in inducing cellular immunity can be a bad vaccine for inducing humoral immunity?

Actually, the immune system is a complex responder to antigen challenges and this is not as simple as it seemingly takes. If the vaccine present antigens properly to induce both humoral and cellular immunity arms, then both arms of immune system will be triggered simultaneously by targeting different non-competitive epitopes [61,62].

Upon using regression analysis of the correlative behavior between IFN-y and the proliferative percentage of PBMC and level of nAbs, the IFN-

y is considered the independent factor on which T cells proliferation and level of nAbs are dependent. Hence, IFN-γ can be used as a predictive marker for the clonal expansion of T cells and the level of humeral immunity. This adds more evidence on the importance of choosing IFN-γ in vitro release studies in understanding the complex relationships of immune responses got by multi-pathway stimulating vaccines.

In conclusion, Pfizer and AstraZeneca vaccines were shown to be quite effective in eliciting both humoral and cell mediated immunity, both arms were robustly activated against SARS-CoV-2 from two doses as early as 1 month. Sinopharm vaccine was shown to be effectively eliciting humeral immune response as early as 1 month after the second dose but it just elicited weak cellular immune response. The neutralizing humeral immune response induced by Pfizer, AstraZeneca, and Sinopharm vaccines was shown to last up to 8 months after the second dose but at significantly reduced level. The cellular immune response induced by Pfizer, AstraZeneca, and Sinopharm vaccines was shown to be maintained and even augmented at 8 months when compared to just 1 month after the second dose of vaccines, maybe due to frequent re-exposures to the virus. AstraZeneca, compared to other two vaccines, showed remarkable capability for priming in vitro peripheral lymphocytes in inducing high levels of IFN-γ, the central cytokine for T-helper1 polarization and antiviral cytotoxicity.

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Author contribution

Jawad: carried out the research. Dr. Abdulamir: designed and research.

Conflict of interest

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