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Original Article

ارزیابی ایمنی سلولی و هومورال در طی واکسیناسیون سینوفارم

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چکیده

سابقه و هدف: در این تحقیق، رویدادهای ایمونولوژیک رخ داده در طول واکسیناسیون با COVID-19 و همچنین مکانیسم‌های سلولی و مولکولی آن مورد مطالعه قرار گرفت. هدف از این مطالعه بررسی ایمنی سلولی و ژن‌های فعال کننده لنفوسیت و همچنین شناسایی تغییرات نشانگرهای سطح لنفوسیت Th در طول دوره واکسیناسیون COVID-19 با واکسن سینوفارم است.

مواد و روش‌ها: در این مطالعه از ۶۰ فرد سالم که در گذشته به کرونا مبتلا نشده بودند، خون گرفته شد و تغییرات CD3 و CD4 در طول واکسیناسیون اندازه‌گیری شد. همچنین سطوح آنتی‌بادی IgM و IgG ارزیابی و میزان بیان ژن‌های *IFN-α* و *IFN-γ* با روش Real time QPCR اندازه‌گیری شد.

یافته‌ها: پس از تزریق اولین دوز واکسن سینوفارم، IgM و IgG به‌ترتیب در ۶۵ درصد و ۶۰ درصد افراد به طور معنی‌داری افزایش یافت. پس از دوز دوم، افزایش قابل توجه ۸۰ درصدی برای هر دو آنتی‌بادی در شرکت کنندگان مشاهده شد. درصد لنفوسیت‌های $TCD3^+$ پس از اولین دوز واکسن کاهش (۲۵٪)، بدون تغییر (۱۵٪) و افزایش (۶۰٪) نشان داد. این فراوانی پس از دومین دوز به‌ترتیب ۱۵، ۱۵ و ۷۰ درصد بود. پس از اولین دوز واکسن، کاهش ۲۰ درصدی درصد لنفوسیت‌های $TCD4^+$، عدم تغییر در ۳۰ درصد و افزایش قابل توجه در ۵۰ درصد مشاهده شد. پس از دوز دوم، این مقادیر به ترتیب ۲۰، ۲۰ و ۶۰ درصد تعیین شد.

نتیجه‌گیری: نتایج آزمایشات واکسن Sinopharm نشان دهنده ایجاد آنتی‌بادی‌های خنثی کننده قوی و تخصصی در اکثر افراد است. علاوه‌براین، دوز تقویت کننده واکسن تحریک بالای سلول‌های ایمنی اختصاصی را نشان می‌دهد.

واژگان کلیدی: ویروس کرونا، کووید-۱۹، لنفوسیت‌ها، واکسن، سینوفارم.

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Evaluation of cellular and humoral immunity during Sinopharm vaccination

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Abstract

Background & Objectives: In this research, the immunological events that occurred during vaccination with COVID-19 as well as its cellular and molecular mechanisms were studied. The purpose of this study is to investigate cellular immunity and lymphocyte activating genes, as well as to identify changes in Th lymphocyte surface markers during the period of COVID-19 vaccination with Sinopharm vaccine.

Materials & Methods: In this study, blood was taken from 60 healthy people who had not been infected with corona in the past , and CD3 and CD4 changes during vaccination were measured. Also, IgM and IgG antibody levels were evaluated, and real time QPCR method was used to measure the expression level of *IFN-α* and *IFN-γ* genes.

Results: The results showed that after the injection of the first dose of Sinopharm vaccine, IgM and IgG increased significantly in 65% and 60% of people, respectively. After the second dose, a significant increase of 80% was observed for both antibodies in the participants.The percentage of $TCD3^+$ lymphocytes decreased (25%), remained unchanged (15%) and increased (60%) after the first dose of vaccine. This frequency after the second dose was 15, 15 and 70% respectively. After the first dose of vaccine, there was a 20% decrease in the percentage of $TCD4^+$ Lymphocytes, no change in 30% and a significant increase in 50%. After the second dose, these values were determined as 20, 20 and 60%, respectively.

Conclusion: The results of the Sinopharm vaccine trials show the creation of strong and specialized neutralizing antibodies in most persons. Additionally, the booster dose of the vaccine ensures a high stimulation of memory cells.

Keywords: Coronavirus, COVID-19, lymphocytes, Vaccine, Sinopharm.
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Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*) caused the COVID-19 pandemic. The first case of COVID-19 was reported in Wuhan, China in early December 2019. Testing biological samples for specific antibodies to *SARS-CoV-2* before December 2019 would provide clues as to when the *SARS-CoV-2*

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epidemic would circulate in the population (1).

Coronaviruses are positive single-stranded RNA viruses belonging to the Coronaviridae family, which are divided into four genera based on their genetic characteristics: alpha-delta and gamma-coronaviruses, and beta-coronaviruses, that infects lung epithelial cells by first binding the viral S glycoprotein to its receptor, angiotensin-converting enzyme (ACE2). Lung epithelial cells are the first cell type to initiate the innate immune response to COVID-19 by secreting interleukin-8 (*IL-8*) and attracting neutrophils (2).

SARS-CoV-2 uses the cellular serine protease TMPRSS2 to enter lung cells so TMPRSS2 inhibitors are being developed for COVID-19 treatment. However, the *SARS-CoV-2* omicron variant currently dominating the pandemic prefers the endo/lysosomal cysteine protease cathepsin L over TMPRSS2 for cell entry (3).

Transmission through infected droplets and direct contact between two people are the most common routes to get infected with *SARS-CoV-2*, which can affect many cell types, especially the lungs, heart, kidneys, and male gonads.

Levels of *IL-ß1*, *IFN-γ*, *IL-6*, and monocyte chemoattractant protein 1 (MCP-1) are all associated with COVID-19 disease severity; as cytokine storm remains the leading cause of death in COVID-19, therapeutics have been proposed. Cytokine storm is due to an acute hyperinflammatory response, and is responsible for the clinical manifestations of many diseases, but in COVID-19 it is associated with poor prognosis and increased mortality (4).

The whole genome of SARS-CoV-2 was sequenced during the initial stages of the outbreak. The sequences exhibited a high degree of similarity, with a 79.6% sequence identity to SARS-CoV. Furthermore, it has been demonstrated that SARS-CoV-2 shares 96% genome-wide identity with a coronavirus found in bats (5).In most infectious diseases, T cell responses are strongly directed against virus-specific proteins, and target cells differ greatly between $CD4^+$ and $CD8^+$ T cells. *SARS-CoV-2* proteins and epitopes recognized by human T cell responses are strongly associated with target cells. The information obtained about the epitope aids in the development of vaccine candidates and facilitates assessment of the immunogenicity of the vaccine in question. Almost all current COVID-19 vaccine candidates focus on the spike protein (6).

SARS-CoV-2-specific T cells consist of a subset of T cells that can recognize specific viral epitopes. Specific $CD4^+$ T cells are important for generating strong B cell responses that lead to antibody maturation, and the concentration of specific T cells correlates with serum IgG and IgA titers. Patients who have recovered from COVID-19 infection display a strong immune response with specific neutralizing antibodies, memory B cells, and circulating TFH cells (7).

CD4+ T cells have the ability to differentiate into various types of helper cells. Virus-specific CD4+ T cells normally differentiate into Th1 cells and follicular T helper cells (TFH). Th1 cells have antiviral activity through the production of *IFN-γ* and related cytokines. TFH cells are helper cells and specialized suppliers of B cells, essential for the further development of neutralizing antibody responses, formation of memory B cells, and long-term humoral immunity (8). Lymphocytopenia with reduced CD4+ T cell counts is one of the disease manifestations of COVID-19 and is associated with decreased T cell proliferative capacity

and elevated levels of pro-inflammatory cytokines (9).

The humoral response to *SARS-CoV-2*, like other coronavirus infections, involves the production of IgG and IgM (10). These two antibodies which are primarily against *SARS-CoV-2* Targeting nucleocapsid and spike proteins (11). IgM and IgA antibodies are detected 5 days after the onset of early symptoms, whereas IgG is detected after 14 days (12).

Generating neutralizing antibodies against *SARS-CoV-2* is relatively straightforward as a wide range of B cells produce antibodies with little or no affinity maturation. Data also indicate that *SARS-CoV-2* neutralizing antibody responses are generally generated by naive B cells, not by cross-reactive memory cells (13,14,15).

Immunization by vaccine is one of the greatest achievements of modern medicine. Conventional vaccines often take more than 15 years to develop from initial design to clinical trials (16,17).

Careful testing and monitoring are essential to ensure that vaccines are safe. However, due to the seriousness of the disease and the urgent need for treatment and prevention, several vaccine candidates for COVID-19 entered clinical trials within six months after the COVID-19 outbreak began and were approved within 10 months. This speed showed a record-breaking speed in the history of vaccine development (16,18).

Currently, there are 199 and 183 candidate vaccines undergoing preclinical development and various clinical stages, respectively. Also a total of 50 vaccines have received approval for use across 201 countries, and 12 vaccines have been granted Emergency Use Listing (EUL) by the World Health Organization (WHO) (19).

Compared with live-attenuated vaccines, inactivated vaccines such as Sinopharm, are less effective and inducing primarily antibody-mediated immune responses and minimal cell-mediated immune responses (20,21).

Furthermore, apart from the primary surface antigens, this vaccine incorporates supplementary structural proteins, thereby enhancing the immune response. Additionally, it offers numerous benefits compared to other vaccine types, particularly in terms of development and production, making it especially advantageous for low-income and developing nations. Notably, during the COVID-19 pandemic, at least half of the vaccines being utilized are inactivated, including CoronaVac and Sinopharm BIBP-COVID-19 vaccines, which are commonly administered in Southeast Asian and Latin American countries (22).

To make Sinopharm vaccine, the virus is grown in Vero cells and inactivated with β-propiolactone (BPL). The production of the Sinovac vaccine involves several steps of virus purification, resulting in a product consisting mostly of viral proteins and pure virus particles. Aluminum hydroxide is used as an adjuvant for this vaccine (22).

The purpose of this study is to investigate the function of the cellular and humoral immune system in people vaccinated with Sinopharm vaccine, as well as to investigate surface changes of T lymphocyte markers after vaccination, to investigate cellular immunity in COVID-19 vaccination and to identify changes in surface markers during COVID-19 vaccination and Investigating T lymphocyte active genes in COVID-19 vaccination.

Material and method

This study was conducted from January 2022 to September in Shiraz City. To conduct this study, blood samples were taken from 60 healthy people who had not been infected with corona in the past after obtaining the code of ethics and consent form. For this purpose, from the participants on 3 occasions, before the injection of the vaccine (sample zero), and 21 days after the injection of the first and second doses of the vaccine (sample one and two), sampling was done.

Evaluation of IgM, IgG and *IL-6* antibodies was done by ELISA method according to the manufacturer protocol. Peripheral blood mononuclear cells (PBMC) were isolated for immunophenotyping using real-time PCR and Ficoll. We examined the immunophenotype of CD4 and CD8 markers on PBMCs using flow cytometry methods. Briefly, after isolation of PBMCs, CD4-FITC and CD8-PE monoclonal antibodies were added to microfuge tubes and incubated in the dark at 4°C for 30-45 min before cell percentage was determined by flow cytometry (23).

To perform real-time PCR, RNA was extracted using RNA extraction kit (Yekta tajhiz, Iran) from PBMC cells, and the purified RNA was converted to cDNA using cDNA synthesis kit (Yekta tajhiz, Iran).

First, the materials required for cDNA synthesis were poured into a Rnase-free microfuge tube, mixed well, vortexed, and loaded into the PCR machine according to the program.

Materials needed for cDNA synthesis were as fallow: Template RNA (1-5 µl), Buffer-Mix (10 µl), Enzyme Mix (2 µl), DEPC-treated water (Up to 20 µL). PCR program for cDNA synthesis 10 minutes 25˚C, 60 minutes 47 ˚C, 5 minutes 85˚C.

Primers for the *IFN-α* and *IFN-γ* genes and GAPDH as internal control were designed from the PRIMER BLAST site and using the SYBR-Green (Roche, Germany) method. The designed primers were then purchased from Sinacolon, and the GAPDH internal control gene was purchased from Metabion (Table 1).

Table 1. Designed primer for cytokine gene expression.

Gene	Primer
IFN-α F	5'-GACTCCATCTTGGCTGTGA-3'
IFN-α R	5'-TGATTTCTGCTCTGACAACCT-3'
IFN-γ F	5'-TGACCAGAGCATCCAAAAGA-3'
IFN-γ R	5'- CTCTTCGACCTCGAAACAGC-3'
GAPDH F	5'-GAGCCAAAAGGGTCATCATC -3'
GAPDH R	5'-TAAGCAGTTGGTGGTGCAGG -3'

Table 2. Real time PCR program.

Stage	Tm (ºC)	Time	
Enzyme Activation	95	15 Min	
First Denaturation & Holding	95	20 Sec	
Annealing	55-65	30 Sec	35 cycles
Extension	72	30 Sec	
Melting	65-95	Each 1 sec 5 degrees	

Statistical Analysis: SPSS software, version 27 for statistical analysis and GraphPad Prism software (version 9) for graph plotting were used. All tests were repeated three times for each sample. Relative expression levels of the investigated genes were measured and the results were evaluated using 2-ΔΔCt method. Normal distribution of data was checked using the Kolmogorov-Smirnov test. Two data groups were compared using independent t-tests and more than two groups were compared using one-way ANOVA. For non-normal samples, the Mann-Whitney and Kruskal-Wallis nonparametric tests were used. P-values less

than 0.05 were considered significant in this study. Informed Consent: Informed consent forms were obtained from the patients.

Results

After injecting the first dose of Sinopharm vaccine, the level of IgM and IgG antibodies remained unchanged in 35% compared to pre-vaccination and was significantly increased in 65% of individuals. After the second dose, this amount remained unchanged in 20%, whereas a significant increase in both antibodies was observed in 80% of the participants (Table 3).

Table 3. Changes in IgM and IgG levels during Sinopharm vaccination.

		IgM		IgG	
	Dose of	—	↑	—	↑
Sinopharm	1st	35%	%65	35%	65%
	nd2	20%	%80	20%	80%

Percentages of T lymphocyte markers including CD3 and CD4 before injection of the Sinopharm vaccine were 58 ± 4.5 and 35 ± 2.8, respectively. After the first dose, this amount did not change significantly, while after the second dose, this amount increased significantly (Table 4).

Specifically, after the first dose of vaccine, the percentage of TCD3+ and TCD4+ lymphocytes decreased in 25% and 20% of subjects, remained unchanged in 15% and 30%, and decreased in 60% and 50% of subjects, respectively. After the second dose, the percentage of these lymphocytes decreased in 15% and 20% of subjects, respectively, remained unchanged in 15% and 20%, and increased significantly in 70% and 60% (Table 5).

Flow cytometry was used to examine the changes in $TCD3^+$ and $TCD4^+$ lymphocytes during vaccination with Sinopharm vaccine. The changes in $TCD3^+$ and $TCD4^+$ lymphocytes are shown in Figure 1. The percentage of T lymphocyte markers including CD3 and CD4 before the injection of Sinopharm vaccine was 58±4.5 and 35±2.8, respectively, after the first dose injection, it was 62±3.8 and 38±4.2, respectively, and after the second dose injection, it was 66±3.2 and 41±2.8, respectively. The increase in CD3 and CD4 markers after the first and second doses of Sinopharm vaccine was significant.

After the first dose of vaccine, the percentage of $TCD3^+$ lymphocytes decreased in 25% of subjects, remained unchanged in 15% of

Table 4. Percentage of TCD3+ and TCD4+ lymphocytes before and after injection of Sinopharm vaccine.

	CD3			CD4		
	0 th	1 st	2 nd	0 th	1 st	2 nd
Sinopharm	58±4.5*	62±3.8*	66±3.2**	35±2.8*	38±4.2*	41±2.8**

Table 5. Changes in TCD3+ and TCD4+ lymphocytes before and after injection of the Sinopharm vaccine.

Marker		CD3			CD4		
	Dose of vaccination	↓	—	↑	↓	—	↑
Sinopharm	1st	25%	15%	60%	20%	30%	50%
	2nd	15%	15%	70%	20%	20%	60%

subjects, and increased in 60% of subjects. After the second dose, the percentage of these lymphocytes decreased in 15% of people, remained unchanged in 15% of people, and significantly increased in 70%. After the first dose of the vaccine, the percentage of $TCD4^{+}$ lymphocytes decreased in 20% of people, remained unchanged in 30% of people, and significantly increased in 50%. After the second dose, the percentage of these lymphocytes decreased in 20% of people, remained unchanged in 20% of people, and significantly increased in 60% (Figure 1).

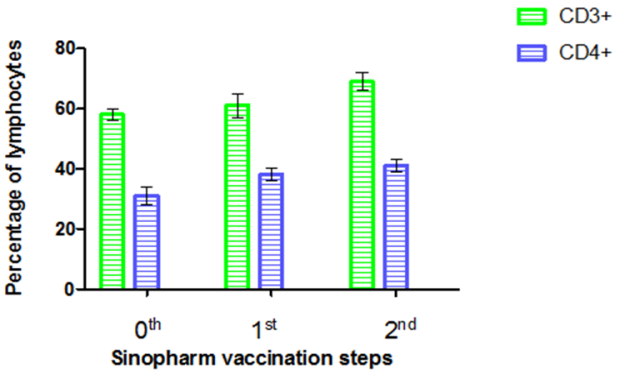

Figure 1. Percentage of TCD3+ and TCD4+ lymphocytes before and after injection of Sinopharm vaccine.

The expression levels of *IFN-α* and *IFN-γ* genes are shown in figure 2. Injection of the first dose of Sinopharm vaccine did not affect gene expression of these cytokines. On the other hand, the second dose of the Sinopharm vaccine significantly increased the expression of the *IFN-α* cytokine gene. Also the Injection of the first and the second doses of Sinopharm vaccine significantly increased the expression of *IFN-γ* gene. In general, the results of this study indicated that the Sinopharm vaccine has an excellent ability to stimulate cell-mediated immunity and increase gene expression of *IFN-α* and *IFN-γ* cytokines (Figure 2).

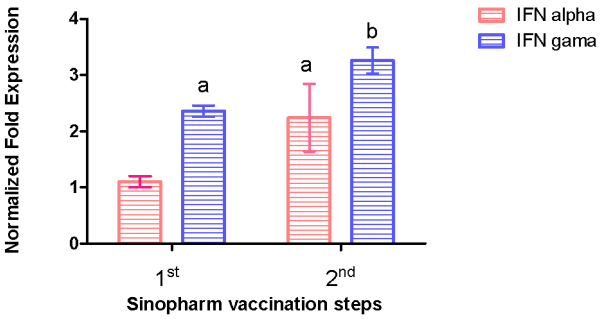

Figure 2. Gene expression of *IFN-α* and *IFN-γ* genes after two doses of Sinopharm vaccine injection. The results are presented as mean ± SEM (* $P < 0.05$).

Discussion

Corona has a dual function on the immune system. This function can be different depending on how the immune system is activated and the genetic differences of people. In some individuals, the activation of the immune system by this virus induces a protective response against it and effectively eliminates the virus. In some other persons, this activation destructive effects for the host. Vaccination against Corona can make it clearer to understand how the immune system deals with this disease (24).

Our study examined humoral and cellular immune responses in 60 subjects who received two doses of the Sinopharm vaccine. The results showed that the vaccine has the ability to increase TCD4+ and TCD8+ lymphocytes after the first and second doses of the vaccine. Induction of Th and Tc lymphocytes, which play an important role in cellular immunity and providing protection against this virus, can be an important factor in fighting this disease.

It is known that people with a mild form of the disease have an increase in TCD4+ and TCD8+ cells (25), whereas a significant decrease in these lymphocytes is observed in patients with severe disease (26). Declining TCD4+ cell counts have also been found to be critical for

coronavirus patients (27).

Decrease in the number of TCD8+ and TCD4+ cells in severe cases of the disease can be due to the viral mechanisms which reduce the number of lymphocytes. while in the case of vaccines, they are subunit type or killed and these mechanisms do not exist so an increase in the number of lymphocytes is observed (28).

A similar study in Chile in 2021 shows similar results when looking at the inactivated coronavirus vaccine. In the study an increase in the number of *IFN-γ* secreting T cells was observed on days 28 and 42 days after vaccination compared to day 0. On the other hand, the number of activated T cells increased in vaccinated subjects 28 days after vaccination compared to day 0 (29).

The humoral immune response, especially neutralizing antibodies, is a key component of acquired immunity against acute cytopathic viruses such as *SARS-CoV-2* (30).

In line with the investigation of humoral immunity, it was found that the injection of vaccine and booster doses increases the number of B cells in peripheral blood mononuclear cells (PBMC), which can be very effective in producing neutralizing antibodies (31).

The amount of *SARS-CoV-2* antigen-specific serum IgG as well as virus neutralization potential was investigated in people vaccinated with five different COVID-19 vaccines, including mRNA, virus vector and inactivated vaccines. Among the 5 vaccines examined, the Sinopharm vaccine had a lower ability to induce neutralizing antibodies, and on the other hand, the least side effects among the 5 vaccines studied were observed in the Sinopharm vaccine (30).

It is shown that RNA-based COVID-19 vaccines based on *adenovirus* and inactivated vaccines, were effective in inducing humoral and cellular immune responses, although both responses were against S protein, the humoral response was not strongly correlated with the cellular response (32).

Moreover, studies have shown that *SARS-CoV* can suppress the type I IFN response using different mechanisms (33,34).

However, the results of our study showed that vaccines, unlike natural infections, have a high ability to produce IFNs, including *IFN-γ*. It seems that the rapid replication of the virus suppresses the expression of type 1 interferon, while its weakly pathogenic form increases its activity, similar to the effect of the vaccine (35).

Studies have shown that after the injection of various vaccines, such as NVX-CoV2373 (36), CoronaVac (31), and (Ad5-nCoV) (37), an increase in Th1 cells is observed. The comparison with Th1 changes in our study, the results of CD3 and CD4 increased after the second dose. Increases in CD3 and CD4 markers were significant after the first and second doses of Sinopharm vaccine .

In one study, the response to BNT162b2 mRNA vaccine against *SARS-CoV-2* was evaluated in the first six months after vaccination in lactating women and normal and positive subjects. After the injection of the second dose, the expression of *IFN-γ* in peripheral blood lymphocytes, CD3+ T cells and serum increased, as well as the serum level of anti-RBD IgG up to 2 months after vaccination. In this study, the results showed that CD4 T cells were mainly activated after mRNA vaccination. In this study, no significant difference was observed in the serum levels of *IL-6* and *TNF-α* 7 days to 1 month after complete vaccination, which may be due to the sampling time (36). This is in agreement with

our findings with the Sinopharm vaccine for these two cytokines (data not shown).

In another study, volunteers vaccinated with a *SARS-CoV-2* vaccine (CoronaVac) were followed for T-cell immune responses after the end of a randomized phase III clinical trial. Accordingly, proliferation and *IFN-γ* secreting capacity decreased after 4 months, and CD4+ and CD8+ cells obtained from Corona Vac-vaccinated volunteers also up-regulated molecules associated with immune activation and regulation (37).

Another study evaluated T-cell immune responses in volunteers vaccinated with the *SARS-CoV-2* vaccine (CoronaVac) after the completion of a randomized Phase III clinical trial. Thus, proliferation and *IFN-γ* secretion capacity decreased after 4 months, and CD4+ and CD8+ cells from CoronaVac-vaccinated volunteers also upregulated molecules associated with immune system activation and regulation (37).

In one study, a patient received a fourth dose of Sinopharm and had only a modest increase in neutralizing antibody levels despite normal levels. Neutrophils and lymphocytes showed high levels of anti-RBD IgG months after the last vaccination, but the patient had no symptoms of *SARS-CoV-2* infection and this increase was within 3 months (38). The extent of immunoglobulin changes after vaccination was examined. The findings showed 85.7% of Sinopharm vaccinees were IgG positive (39).

Conclusion

So far, various platforms are investigated for the production of the COVID-19 vaccine and each of these platforms has unique advantages and disadvantages. It is highly likely that the world will need more than one type of approved vaccine to combat this pandemic, ensuring broad coverage of the target population, production quantities, and storage and transportation requirements along with vaccine safety and efficacy.

Various platforms for manufacturing COVID-19 vaccines have been explored to date, each with its own strengths and weaknesses. It is highly likely that the world will need multiple licensed vaccine types to effectively combat this pandemic, covering a wide range of production volumes, storage and transportation requirements.

It is essential to understand that the virus can deceive the immune system in weak and susceptible individuals, preventing the immune system from mounting appropriate responses. This can lead to the development of deadly forms of COVID-19. In contrast, vaccines do not cause such deception; instead, they usually contain substances that stimulate the immune system.

Vaccines provide a fixed and specific dose, creating a uniform immunity among the vaccinated population. However, in about one-third of recovered individuals who have produced a large number of antibodies, these antibodies may not provide stable and neutralizing immunity. Additionally, some of these antibodies can be pathogenic, and memory cells might not be adequately stimulated.

It is not known the viral load enters the body and the severity of illness when contracting COVID-19. Vaccines, on the other hand, provide a fixed and specific dose, ensuring a more uniform immunity in the vaccinated population. In many recovered individuals (approximately one-third), despite the development of numerous antibodies, these antibodies do not display stable neutralizing immunity. Research has shown that this type

of antibody production, more than usual, can be formed by extrafollicular B lymphocytes outside the germinal centers of the lymph nodes. These lymphocytes have potential to be pathogenic, and memory cells might not be stimulated sufficiently (40).

The published results of the Sinopharm vaccine trials show the creation of strong and specialized neutralizing antibodies in most persons. Additionally, the booster dose of the vaccine ensures a high stimulation of memory cells. The risk of contracting COVID-19 may lead to severe illness, pain, suffering, and even death. However, as of today, no cases of very severe uncontrollable side effects or death because of the Sinopharm vaccine have been reported.

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Ethical Considerations

The authors of this article have observed all ethical principles, such as avoiding plagiarism, maintaining literary standards, simultaneous publication, and refraining from data manipulation and fabrication.

Conflict of interest

The authors declare that they have no conflicts of interest.

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