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## Original article

# The effectivity of Pfizer vaccine on oral immunological biomarkers sIgA and interleukin-21

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## ABSTRACT

**Background:** The most widely used vaccination against SARS-associated coronavirus (SARS-CoV-2) is the Pfizer vaccine, which provides protection against this virus. However, its ability to safeguard the oral cavity is unclear, and neither are the exact immunological biomarker levels it activates. This study aims to detect if the Pfizer-BionTech covid-19 vaccine protects the oral cavity after vaccination by estimating the salivary sIgA levels, IL-21 in saliva for subjects before and after vaccination with the Pfizer covid-19 vaccine. **Methods:** In this cross-sectional study, 70 subjects were followed up: the non-vaccinated individuals served as the control group, and those who received the first and second doses of the vaccine constituted the study group. The salivary biomarkers sIgA and IL-21 were detected using enzyme-linked immunosorbent assay (ELISA) kits. **Results:** The current study showed a highly significant ( $p=0.0001$ ) in secretory-IgA levels after the first vaccination in follow-up compared with non-vaccinated in same subjects (as control), while a non-significant when compared with after second vaccination groups. However, salivary IL-21 levels showed highly significant differences between the non-vaccinated follow-up comparing with after first and after second vaccination also compared the first with second followed up groups reflect an increased and highly significant difference ( $p<0.001$ ). **Conclusion:** The current study shows that the Pfizer vaccine has a minimal impact on sIgA levels due to its primary role in systemic rather than local salivary protection. However, a rise in IL-21 was observed after the first dose in non-infected participants, indicating its systemic protective effectiveness, which stabilizes after the second dose.

## Introduction

In December at 2019, Wuhan in China was the first city to report a case of COVID-19, viruses belonging to the family Coronaviridae are enclosed ssRNA viruses with spike-like glycoproteins; their encoding proteins, S, M, E, and N, are important for viral entrance, replication, diffusion, and protection, the S protein, a primary vaccine target, consists of

three critical parts: S1, the receptor binding domain (RBD), and the S2 subunits [1]. Damage to the respiratory system and other organs is caused by coronaviruses, which may be associated with the distribution of ACE2 receptors (angiotensin converting enzyme-2) in the human body. These receptors may be found in the salivary glands, the mucosa, and the tongue [2]. Oral mucosa infections

cause damage to the epithelium and trigger inflammatory responses at the site of infection [3]. Xerostomia is one of the most significant ways in which COVID-19 impairs oral health, tooth decay, oral mucous membrane irritation, fissures, and cheilitis are all possible consequences of xerostomia, as are Sialadenitis, ulcers, tongue, and buccal mucosa edema oral candidiasis, and enlargement of the parotid gland [4]. The disease might manifest with no outward signs, show mild to severe symptoms, or even be fatal and, The current COVID-19 pandemic is the worst since the Spanish flu in 1918, As a result of the ongoing pandemic, a vaccine is needed to provide lifelong protection against the virus [5]. Researchers demonstrate antibodies in the saliva including IgG, IgM, and IgA have a potential role against covid-19, in the patient's in the acute and convalescent stages of illness against the spike protein of SARS-CoV-2 as well as the RBD of SARS-CoV-19, and this antibody function in neutralizing the virus and providing the host with protection against re-infection by viral duration and efficacy of protection [6,7]. Actually, Saliva contains a number of minerals, stress hormones such as cortisol, proteins, anti-microbial peptides, lysozymes, and immunoglobulins particularly the secretory IgA (S-IgA) that performs an essential function in the fight against SARS-CoV-2 [8,9]. Secretory IgA is an essential immunological biomarker that neutralizes and restricts the adhesion and invasion of epithelial cells, In addition, it can agglutinate and facilitate the clearance of the pathogen including viruses in mucus secretion [10]. Its presence in the upper and lower respiratory tracts may be crucial in warding off infection with the SARS-CoV-2 virus, which targets the epithelium lining the respiratory tract and causes pneumonia, using the polymeric immunoglobulin receptor, also known as pIgR, is a protein that is found on the basolateral side of epithelial cells, thus SIgA antibodies (IgA antibodies) are made in the mucosal stroma and transferred to the mucosal surface. The secretory component (SC) of the pIgR is integrated into IgA molecules prior to their release to the mucosal surface to combat the spread of covid-19 infection The polymeric immunoglobulin receptor mediates transcytosis IgA is secreted into the oral cavity at a certain point throughout the infection, which involves passing through the cytoplasm of mucosal epithelial cells (pIgR). Secretory IgA (sIgA) is produced locally and is a dimer of IgA that coats

mucosal surfaces by binding to the (SC). furthermore, SIgA can provide Protection to the mucosal lining against local commensal bacteria' enzymatic breakdown and degradation [11]. Although a mucosal sIgA response was elicited by vaccinations given intramuscularly, the exact mechanism through which this occurred is unknown. Antigen-specific B cells that have expanded in the spleen or peripheral lymph nodes may move to the mucosa-associated lymphoid tissue (MALT) to generate a mucosal antibody response that may use their homing receptors to migrate to mucosal sites, where they will differentiate into plasma cells and secrete antibodies [12]. Furthermore, the study found that multiple vaccinations and breakthrough infection can affect SARS-CoV-2 S-specific circulating IgA. Two mRNA-based vaccinations induce systemic IgA anti-FLS and anti-RBD responses, while a third vaccination boosts this response. However, the third vaccination's increase is less significant than the breakthrough infection. Higher levels of vaccine-induced anti-SARS-CoV-2 S IgA after three vaccinations reduce the risk of breakthrough infection [13].

One possible explanation is that the early-phase systemic IgA response in these cases reflects the production of natural antibodies from activation of B1 B cells expressing IgA [14].

The Pfizer vaccine improved for trigger immune responses, there was just a mild innate immune response 1 or 7 days following the first vaccination, which the recruitment and activation of neutrophils, monocytes, macrophages, dendritic cells (DC), natural killers (NK), and innate lymphoid cells into the infection site is caused by the release of soluble substances, such as proinflammatory cytokines and chemokines, from local immune cells and infected epithelial cells [15].

Interestingly, a supplementary BNT162b2 immunization elicited a more robust innate immune response than the first vaccination, even Myeloid cell antiviral immunity and innate immune transcriptional markers were both augmented, as was the production of IFN- $\gamma$  in the body, A subsequent vaccination may boost the innate immune response, although it is unknown where this IFN- $\gamma$  comes from in the body or what function it plays in this process. Moreover, BNT162b2 immunization has been demonstrated to produce significant frequencies of antigen-specific CD8+ T

cell responses [13]. While In response to SARS-CoV-2, cells such as macrophages and dendritic cells may deliver antigen fragments to naïve CD4+ T cells, then upon activation, APCs produce polarising cytokines TGF-B, IL-6, and IL-23. In turn, IL-6 binds to its receptor and, through JAK-STAT3, induces the polarisation, maturation, and proliferation of CD4+ T cells into Th17 cells via the expression of ROR t. In response, the activated Th-17 cells generate inflammatory cytokines such as IL-21, IL-22, IL-17A, and IL-17F [14]. The type I cytokine IL-21 is secreted by T cells and natural killer T cells and has pleiotropic activities on many different kinds of immunological and non-immune cells, Many in vivo and in vitro which investigations on a biological effects of the IL-21 have been conducted since its discovery in the year 2000 [15]. And when the B cells subsequently specialize into plasma cells, which generate and secrete huge amounts of these antibodies at sites of infection and throughout the body's circulation. Interleukin-21 (IL-21) promotes B-cell proliferation in germinal centers. IgA, IgG3, and IgG1 antibody class switching are all supported by IL-21.

IgA is primarily active in the mucosal immune system, where it blocks viral attachment to epithelial cells. Neutralizing antibodies might be either IgA or IgG. Antibody-making plasma cells have been shown to benefit from IL-21's ability to promote their development and proliferation of antibodies [16]. Therefore, the aim is to specifically investigate the protective effect of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine on the oral cavity by measuring the levels of salivary secretory immunoglobulin A (sIgA) and interleukin-21 (IL-21) at three distinct time points: before immunization, three weeks after the first dose of the vaccine, and one week after the second dose.

### Materials and methods

The cross-sectional study was conducted in medical city of Baghdad, Iraq, between January and July 2022. The study involved seventy participants aged between 20 and 60 years who were followed up, the non-vaccinated individuals served as the control group, and when who received the first and second doses of the vaccine constituted the study group. Ethical approval was obtained from the scientific committee at the Basic Science Department/College of Dentistry/University of Baghdad (Project No. 2021-406).

### Inclusion criteria

The Inclusion criteria for this study included participants aged between (20-60) years old, of both genders.

### Exclusion criteria

The exclusion Criteria in this included alcoholic, patients with comorbid conditions (diabetes mellitus, cardiovascular diseases, pregnancy, chronic kidney disease, chronic lung disease, and patients who had immunosuppressive conditions) were excluded.

### Sample collection

Approximately, one to three milliliters of whole unstimulated saliva was collected for the same participant at three different times: before immunization, 3 weeks after the first dose of vaccinations, and 1 week later after the second vaccination. The participants in the current study were provided with a special case sheet for questioners and abstained from meals before half-hour to avoid contamination, and to reduce diurnal fluctuations associated with saliva collection, all samples were obtained between 9 a.m. and 12 p.m. and each saliva sample was transferred into a sterile plain tube and centrifuged for 15 minutes at 2000 rpm. The supernatant was collected in an eppendorf tube, and all samples were kept in the deep freezer at (-80°C) until analysis [17].

### Enzyme-linked immunosorbent assay (ELISA)

Detection of pro-inflammatory biomarkers by using Human ELISA quantitative immunoassay kit (Secretory IgA/Catalog No: ELK1844, BIOTECH/Uncaria) and (Interleukin-21/Catalog No: ELK2146, BIOTECH/Uncaria) in saliva samples by ELISA reader (BioTek/USA).

### Principle of the procedure

This kit uses sandwich enzyme immunoassay. This package includes a microtiter plate pre-coated with either secretory IgA or interleukin-21 antibody. Microtiter plate wells containing standards or samples get a biotin-conjugated sIgA or IL-21 antibody. Incubate microplate wells with avidin-HRP. TMB substrate solution only colors wells containing sIgA or IL-21, biotin-conjugated antibodies, and enzyme-conjugated avidin. Sulfuric acid blocks the enzyme-substrate reaction, and the color change is measured at 450 nm±10 nm. The concentration of biomarkers in the samples is then determined by comparing the optical density (OD) of the samples to the standard curve.

### Statistical analysis

In this investigation, SPSS version 26, Microsoft excel 2010 were employed. To evaluate the difference between groups, using normality tests, we determined whether the study's data was parametric or non-parametric test. Statistical tests were thus used. One way ANOVA and LSD evaluated differences.

### Results

#### Age and gender among study groups

**Table 1** showed no statistically significant differences in gender and age ( $p=0.0.603$ ) among the study group.

#### Follow-up change of the level sIgA (ng/ml) from non-vaccination to first and second vaccination groups

**Table 2** showed a highly significant difference in the mean value of sIgA (ng/ml) levels in the non-vaccinated group compared with after the first

vaccination group follow-up, the mean $\pm$ SE value is (25.38 $\pm$ 0.432),(20.60 $\pm$ 0.158), ( $p=0.001$ ). On the other hand, the mean value of sIgA in participant with the first vaccinated compared with the second vaccinated follow-up (20.60 $\pm$ 0.158), (and 20.05 $\pm$ 0.216), respectively, was no significant difference ( $p>0.05$ ). As shown in **table (3)**.

#### IL-21 level in non-vaccination follow-up in first and second vaccination groups

**Table 4** showed a highly significant difference in IL-21(ng/ml) levels in participants with non-vaccinated compared with after the first vaccination follow-up, the mean  $\pm$ SE (20.418 $\pm$ 0.942), (502.94 $\pm$ 32.144), respectively, ( $p<0.001$ ). There was also a highly significant difference in the  $p$ . value of IL-21 level in participant who were first vaccinated compared to those who were second vaccinated follow-up (502.94 $\pm$ 32.144), (45.845 $\pm$ 2.9196), respectively, ( $p\leq 0.01$ ). As illustrated in **table (5)**.

**Table 1.** Demographic data of Age and gender among study group

Age	Gender		Total No. (%)	Chi-Square (p. value)
	Female No. (%)	Male No. (%)		
$\leq 40$	20 (43.5%)	26 (56.5%)	46 (100.0%)	0.603 N.S
$> 40$	12 (50.0%)	12 (50.0%)	24 (100.0%)	
<b>Total</b>	32 (45.7%)	38 (54.3%)	70 (100.0%)	

N. S= non-significant

**Table 2.** follow up on the change in sIgA level from non-vaccinated to first vaccination groups

Follow-up group	Mean (ng/ml)	$\pm$ SE	LSD	P. value
<b>Non-vaccinated (as control)</b>	25.38	0.432	4.78*	0.0001
<b>First vaccination</b>	20.60	0.158		

\*=significant at  $p$ -value $<0.05$ ; SE: Standard Error, LSD: Least Significant Difference test

**Table 3.** follow up on the change in sIgA level from first vaccination to second vaccination groups

Follow-up group	Mean (ng/ml)	$\pm$ SE	LSD	P. value
<b>First vaccination</b>	20.60	0.158	0.55	0.252
<b>Second vaccination</b>	20.05	0.216		

non-significant at  $p.>0.05$ ; SE: Standard Error, LSD: Least Significant Difference test

**Table 4.** follow up on the change in IL-21 (ng/ml) concentration from non-vaccinated to first vaccination groups

Follow-up group	Mean (ng/ml)	±SE	LSD	P-value
Non-vaccinated (as control)	20.418	0.942	482.52*	0.0001
First vaccination	502.94	32.144		

\*=significant at  $p$ -value<0.05; SE: Standard Error, LSD: Least Significant Difference test

**Table 5.** follow up on the change in IL-21 (ng/ml) concentration from first vaccination to second vaccination groups

Follow-up group	Mean (ng/ml)	±SE	LSD	P. value
First vaccination	502.94	32.144	457.095*	0.0001
Second vaccinated	45.85	2.9196		

\*=significant at  $p$ -value<0.05; SE: Standard Error, LSD: Least Significant Difference test

## Discussion

The newly discovered respiratory virus known as Covid-19 is very infectious and has been shown to spread quickly and globally. Many governments were unprepared for its outbreak. Some countries have controlled the virus, however, vaccines were developed quickly to avoid this pandemic infection and control the viral spread. One of the First WHO emergency vaccines was BNT162b2 [18]. Fortunately, mRNA COVID-19 vaccines can trigger effective immune system pathways that lead to providing successful protective immunization/or protection against SARS-CoV-2 [19]. Actually, showed there were non-significant differences in the age and gender between the non-vaccinated follow-up and the study groups detected in the current study, the non-vaccinated whether males or females, were nearly equal in number to the study group subjects including those being vaccinated or were previously infected and others were not. The mean age of the control group and the study group was  $(34.03 \pm 9.503)$ , and  $(32.80 \pm 9.400)$ . This may be explained owing to the safety of this specific vaccine for use in various age groups, whether younger individuals with a better immunological response or older ones having less immunity. In the fact, the seriousness of having a COVID-19 infection is influenced not only by age and gender, but also by a multitude of systemic problems, underlying illnesses, hereditary influences, and different personal socioeconomic statuses. Although age and gender are known to play a role in the severity of the infection with covid-19 [20]. And other research by

Jensen et al. [21] showed no statistically significant differences between males and females vaccinated by Pfizer-BioNTech. In another study the older males who had had the BNT162b vaccine were connected with a lower odds ratio of impaired reactivity and inability to work. Elderly patients (65 years) recorded a higher risk of severe or critical illness, intensive care, respiratory failure, and longest hospitalization, which may be explained by their increased prevalence of comorbidities and inadequate immunological responses to COVID-19, thus also found that the vaccine was less safe due to the development of fever, rash, and regional muscle discomfort. Older individuals might be vaccinated safely due to their immunosenescence [22]. In the current investigation, no significant changes in SIgA levels were found between the non-vaccinated control and followed-up groups besides a substantial reduction in this mucosal antibody after two doses of vaccine. This outcome may be related to the mechanism of vaccine delivery through parenteral routes which stimulate mainly IgG and IgM antibodies and fewer amounts of secretory IgA antibodies which may lead to its limitation and sometimes decreased levels in mucosal locations (upper respiratory tract) [23]. This result agrees with Darwich et al. [24] who stated that the BNT162b2 vaccine allows releasing of SARS-CoV-2-specific immunoglobulin in the saliva which originates from serum back to gingival crevices and then to saliva and found Ig specific to SARS-CoV-2 in both the saliva and the plasma is almost completely lost at three months [24] that found the levels of antigen-specific IgG and IgA in the saliva were significantly

decreased at this time point in comparison to 2 weeks after the second dosage. According to **Mohamed et al.** [25]. Saliva is a crucial biofluid that may offer information on the SARS-CoV-2 mucosal Ab reaction blood antibodies may enter saliva via gingival crevicular fluid, Nevertheless, regional secretory IgA (sIgA) is produced by salivary glands during Ab reactions. Furthermore, **Azzi et al.** [26] showed that the serum IgA concentration of seropositive subjects (SP) people seems to plateau after a single dose of vaccination and does not rise after a second dose. After the second treatment, the concentration of IgA in the seronegative subjects (SN) group increased compared to the SP group. This may be due to the fact that earlier virus exposure may induce a mucosal IgA response comparable to other viral infections before systemic immunity develops. Consistent with this concept, it was revealed that in infected persons, the mucosal IgA response is inversely linked with the degree of symptoms, which is more plentiful in individuals with COVID-19 who did not exhibit any symptoms strengthening their function in preventing viral entry into the body. Other researchers as [26, 27] stated that although vaccination of SARS-CoV-2 induces a weak mucosal response, specific IgG and IgA can be detected in the saliva and nasal fluid after vaccination furthermore, BNT162b2 immunization enhances the production of IgG and IgA serum antibodies which can be detected in plasma and saliva **Nahass et al.** [28] found that quantifying sIgA in the saliva is difficult, and suggests luminex-style bead-based assays to be prone to significant background binding of non-specific salivary IgA. **Tu et al.** [29] found minimal levels of sIgA in saliva, but substantial levels of vaccine-induced IgG. The mRNA BNT162b2 vaccination elicits a robust systemic immune response by dramatically enhancing neutralizing antibody development in serum, but not in saliva. This indicates that this vaccination protocol inadequately stimulates oral mucosal immunity, thus failing to prevent virus acquisition via this route. The current study showed an increased level of salivary IL-21 in the non-vaccinated group compared to the study groups although no significant difference was detected between them. Furthermore, its concentration has recorded a significant decrease in the followed-up group after the second vaccination compared to those after the first vaccination followed-up group. The significance of IL-21 in orchestrating effective

immunological response against viral infections is observed by its potency to induce functional programming for CD8+ T cells thereby enhancing their survival and antiviral activity, besides being the key to the maturation of T helper 17 (TH17) cells, which have a role in the pathology of a variety of inflammatory disorders [30]. Nevertheless, the maturation of natural killer cells and subsequent IFN- $\gamma$  production is induced by IL-21, and when it is combined with IL-15 their pronounced effect is seen as the enhanced proliferation of memory CD8+ T cells. We explain the mechanics behind these cytokines as well as their potential use in the development of antiviral vaccines and therapies [31]. Actually, specific CD4 and CD8 T-cell responses during infection in addition to memory B cells and T-follicular helpers could be identified following recovery in patients infected with COVID-19, indicating that, cellular responses after vaccination might affect overall vaccine efficacy against SARS-CoV-2 by [32]. According to our knowledge, this is the first trial of its kind to examine the impact of a COVID-19 vaccination with salivary IL-21. **Mahil et al.** [33] showed a positive T cell response against spike peptides pool mediated by (IL-21, IL-2, interferon- $\gamma$ ) interleukine in psoriasis patients after reserving the Pfizer vaccine [34]. In addition to **Delahoy et al.** [35] stated that detected a strong antibody response in patients with autoimmune disorders (SLE) within more than 5 days after vaccination with the Pfizer vaccine. While production of IL-17 and IL-21 following BNT162b2 inoculation was delayed.

### Conclusion

In the present study, we demonstrate that the Pfizer covid-19 vaccine has little effect on secretory-IgA, according to the results of the current investigation, the Pfizer COVID-19 vaccination does not have a significant impact on secretory-IgA because the mRNA vaccine action is connected to systemic protection rather than the local salivary protective function in the body however, we noticed a rate of interleukin-21 rising after the first vaccination in the non-infected participants as it was filtered by T- helper 1 activated cells while it maintains the required level after the second vaccination, reflecting its effectiveness as a systemic protector.

### Conflict of interest

The authors declared any conflict of interest.

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