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Evaluation Some Immunological Parameter For Corona Vaccinated people in Babylon-Iraq

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بسم الله الرحمن الرحيم

﴿فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ ۗ وَلَا تَعْجَلْ بِالْقُرْآنِ مِن قَبْلِ أَن يُقْضَىٰ إِلَيْكَ وَحْيُهُ ۖ وَقُل رَّبِّ زِدْنِي عِلْمًا﴾

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Dedication

To God Almighty

To Imam ALHussein peace be upon him……the ship of salvation

To the Awaited Imam Mahdi ……..may God hasten his reappearance

To all my life who supported me and stood by me,……..my family

To everyone who wishes me good luck

Baidaa Shaheed

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I thank God Almighty who with the success of him and thanks to I was able to accomplish this massage.

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Summary

This study was conducted in Babylon governorate during the period from Noember/2021 to January/2022 on (85) vaccinated person with or without previous infection as a test group , in comparison with (35) person recovering from Covid-19 which mentioned as positive control with (30) healthy population (non-infected with Covid-19) as a negative control groups , different parameters were studied to evaluation of immunological status after receiving complete doses of different vaccine.

There was a low level of anti Covid-19 – Immunoglobulin-M antibodies of both vaccinated and control groups ,while increased of Covid-19 –IgG in vaccinated population in comparison with cured patients and healthy control , at Mean ±SD(33.21 ± 16.06 , 20.36 ± 14.0 , 21.47 ± 13.77)in respective manner

The P. Value < 0.05.This result may refer to that vaccination might induce specific IgG production rather than Immunoglobulin-m.When studying the effect of Interleukin-12, Interleukin -15 and Interferon-gamma on study populations there wasa highly increased in Interleukin -12, Interleukin -15 and Interferon-gamma levels in comparison with control groups (cured and healthy) at Mean ±SD of IL-12 (26.24 ± 4.78, 6.0 ± 0.82, 6.04 ± 0.95) The Interleukin -15 level(596.84 ± 60.62 , 294.53 ± 37.06 , 292.80 ± 39.11) , and Interferon gamma (143.29±50.92 , 54.92 ± 12.81).The results of the relation between the age groups and Anti Covid-19 Antibodies (Immunoglobulin G,M) revealed that the age groups (20 - 29 years and > 60 years) have higher level of Anti – Covid-19 Immunoglobulin G , the Immunoglobulin M level shows that no difference in level after comparison with other age groups as well as control and the age groups results of all studied groups adult age group > 60 years have lower level of cytokines (Interleukin -12 Interleukin -15 and Interferon-gamma) in comparison with young and adult age groups.

The search show that there was a difference between vaccinated female have higher level of Anti- Covid-19 Immunoglobulin G antibody rather than male , the specific IgM have no differences at both male and female as well as control samples. The male population have higher level of the cytokines (Interleukin -12, Interleukin -15 and Interferon gamma) level in comparison with female in both vaccinated and control groups (cured and healthy population).

The result show that the smoking population have induced antibody production more than nonsmoking one , while there is no specific Immunoglobulin M antibody differences at all smoking and nonsmoking of both studied and control groups. The level of cytokines (Interleukin -12, Interleukin -15 and Interferon gamma) shows elevated level in smoking groups in comparison with nonsmoking as well as with curid and healthy control groups.

The results show that the non infected vaccinated population has a high level of Anti Covid-19 Immunoglobulin G antibodies in comparison with the infected population while the level of cytokines (Interleukin -12, Interleukin -15 and Interferon gamma) among the infected population after receiving vaccine were higher in comparison with non-infected people and repeated more than one infection , as like as the control groups cured and healthy population, at P Value < 0.05.

The rapid detection of anti- Covid-19 Immunoglobulin G ,M Antibody show positive Immunoglobulin- M antibody in vaccinated population which have high level of Anti Covid-19 Immunoglobulin- G antibody in comparison with infected population and there was association with qualitative antibody at high Immunoglobulin G score with the quantitative level of the anti- Covid-19 – Immunoglobulin G antibody and revealed high titer level that other qualitative score of low and moderate IgG antibody as well as control population.

The results show that the Pfizer vaccine induces more protection than Cinopharm at the cellular and humeral immune reactivity.

There was a direct correlation between Interleukin -12, and Interferon gamma among studied groups as well as there was a direct correlation between Interleukin -12, Interleukin -15 among studied groups as well as an indirect or negative correlation between Interleukin -12, Interleukin -15 and Interferon gamma with anti Covid-19 Immunoglobulin- M antibody level and indirect or negative correlation between and Anti – Immunoglobulin- M antibody level ,while there was a direct or positive correlation between Interleukin -12, Interleukin -15 and Interferon gamma with anti Covid-19 Immunoglobulin- G antibody.

The Receiver Operating Characteristic curve analysis was used to determine of sensitivity and specificity between the qualitative or rapid determination of Immunoglobulin- M and Immunoglobulin- G against Covid-19 virus and quantitative measurement of Immunoglobulin- M and Immunoglobulin- G levels the result show that the Immunoglobulin- G levels are more reliable and specific monitor of the immune response in both vaccinated and control population.

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List of Abbreviation

No	Abbreviation	Term
1	ACE2	Angiotensin-converting enzyme2
2	ARDS	Acute renal damage shock
3	Ad26-SARS	Adenovirus type 26 Vectors - Severe Acute Respiratory Syndrome Coronavirus
4	b-cov	Beta coronavirus
5	BCL2L1/BCL-XCLS	B-cell lymphoma 2 –like protein 1/ BCL2L1 long isoform
6	BCI-2	B-cell lymphoma-2
7	BBIBP-CORV	Sinopharm corona vaccine
8	BNT162b1	Pfizer-BioNTech COVID-19 Vaccine1
9	BNT162b2	Pfizer-BioNTech COVID-19 Vaccine 2
10	Cov	Coronavirus
11	VOCs	variants of concerns
12	ACov	Alpha coronavirus
13	C-terminal	Carboxyl-terminus
14	CTD	C-terminal domain

15	CD	Cluster of Differentiation
16	CDC	Centers for Disease Control
17	ChAdoxI	Chimpanzee adenovirus
18	DPP4	Dipeptidyl peptidase4
19	d-cov	Delta coronavirus
20	DCS	Dentric cells
21	E	Envelope
22	ER	Endoplasmic Reticulum
23	ERGIC	Endoplasmic reticulum-Golgi intermediate Compartment
24	ELISA	Enzyme-linked Immunosorbent assays
25	EMA	European Medic Argency
26	FDA	Food and Drug Administration
27	G-Cov	Gamma coronavirus
28	h ACE2	Human angiotensin-converting enzyme 2
29	HKU	Tylonycteris bat coronavirus HKU4 (Bat-CoV HKU
30	HCOV-NL63	Human coronavirus-
31	IBV	Infections Bronchitis Virus
32	IL	Interleukin
33	IL-15R	Inter leukin-15 Receptor
34	i.m.	Intramuscular

35	IgG-IgM-IgA	Immunoglobulin G,M,A
36	JAK kinase	Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases
37	Kb	Kilobases
38	KDa	Kilodalton
39	MERS COV	M idle East Respiratory Syndrome
40	Mrna	Messenger Ripo Neuclu Acid
41	M	Membrane
42	MHV	Mouse hepatitis virus
43	MSCs	mesenchymal stem cell
44	MAbS	Monoclonal antibodies
45	MERS-COV EMC/2012	MERS coronavirus EMC/2012 (MERS coronavirus Erasmus Medical Center/2012)
46	MERR-COV-NAP	MERS coronavirus National Antimicrobial Prescribing
47	MVA	Measles virus adenovirus
48	MV	Measles virus
49	MHC	Major histocompatibility complex
50	NCov	novel Coronavirus
51	N	Nucleocapsid
52	Nsps	Non-structural proteins
53	NHPs	nonhuman primates

54	NK	Natural killer
55	NC-37	Cellosaurus Cells Line
56	Nabs	Neutralizing antibodies
57	NAPS	National Antimicrobial Prescribing Survey
58	ORF	Open Reading Frame
59	ORF1a	Open read Freeding 1 Alpha
60	ORF1b	Open Reading Freeding 1 beta
61	PKR	Protein kinase RNA
62	RNA	Ribonucleic acid
63	RaTG13	Rhinolophus affinis Tche Gengly 2013
64	RBD	Receptor binding domain
65	RdRp	RNA dependent RNA polymerase
66	RT-PCR	Reverse Transcription-Polymarase Chain Reaction
67	RTC	Replicase-transcriptase complex
68	RDT	Rapid diagnostic tests
69	SARS-COV-2	Serve acut respiratory syndrome Coronavirus
70	S	Spike
71	STAT	Signal transducer and activator of Transcription
72	TGEV	Transmissible gastro enteritis
73	TMPRRS2	Transmembrane serine protease 2

74	TNF	Tumor necrosis factor
75	T-cells	T-lymphocytes
76	Th	T helper cells
77	TNF-alpha	Tumor necrosis factor-alpha
78	3 UTR, 5 UTR	3-Untranslated region ,5-Untranslated region
79	VLps	Virus-like particles
80	VAC	Vaccine
81	WHO	World Health Organization

Chapter One

Introduction

1.1. Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19). SARS-CoV-2 has been spreading worldwide since December 2019, leading to the ongoing COVID-19 pandemic with 234 million infections and 4.8 million deaths by 30 September 2021.Due to pressure of the COVID-19 pandemic, the greatest global efforts have been placed for vaccine development. Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and to protect persons who are at high risk for complications (Sharma *et al*.,2020; Peng *et al*.,2022).

The pandemic of coronavirus disease 2019 (COVID-19) has led to an unprecedented rapid vaccine development and production aimed to prevent the spread of the SARS-CoV-2 virus. The clinical severity of the disease has led to the urgent application and approval of vaccines with phase 3 studies under development, with proven safety results, but with little data regarding immune response, efficacy, and mechanism of action to prevent the disease. In this scenario, the immune mechanisms triggered by SARS-CoV-2 vaccines in healthy populations are not well-known. Studies are limited, especially from laboratories not directly related to the manufacture of vaccines or research teams leading the evaluations of phase 2 or 3 clinical trials (Pascual-Iglesias *et al*.,2021; Tregoning *et al*.,2021).

The current COVID-19 mass vaccination schedule consists of two doses of the vaccines separated by 4 weeks (28 days apart schedule vaccination) (Amirthalingam *et al*.,2021). Recently, a prospective national cohort study reported that using this vaccination schedule, CoronaVac is effective for preventing hospitalization (87.5%), Intensive Care Unit (ICU) admission (90.3%), and Covid-19–related death (86.3%) (Jara *et al*.,2021).

Many questions have arisen about the need of a third booster dose,especially given the absence of detailed and conclusive evidence of the immune responses induced by CoronaVac using the 28-day-apart vaccination. Therefore, in this study, we evaluated the production of neutralizing antibodies, the activation of the cellular response, and the generation of cellular memory induced after CoronaVac 28- day schedule vaccination in a healthy population group independently of the production laboratory. Together, our results indicate that CoronaVac induces a robust humoral immune response and cellular immunity of at least 90 dpi, which can explain prevention of COVID-19 with severe symptoms (Huang *et al*.,2020; Jara *et al*.,2021).

To date, six vaccines have been approved by regulatory agencies for emergency use including (Polack *et al*.,2020). two mRNA-based vaccines, namely BNT162b2 (by Pfizer Inc. and BioNTech SE) and mRNA-1273 (by Moderna), expressing full spike (S) glycoprotein with efficacy rates of 94.1-95% against laboratory-confirmed COVID-19 (Baden *et al*.,2020).

The chimpanzee adenovirus-vectored vaccine, named ChAdOx1 nCoV-19 (by the Oxford University and AstraZeneca Inc.), encoding the full S glycoprotein with an efficacy rate of 70.4%,3 (Voysey *et al*.,2021) .

The human adenovirus-vectored vaccine, namely Ad26.COV2.S (by Johnson and Johnson Inc.), encoding the full S glycoprotein with an efficacy rate of 73.1%,4 (Sadoff *et al*.2021; Peng *et al*.,2022).

Two inactivated vaccines CoronaVac and BIBP (by Sinovac Biotech and SinoPharm) with efficacy rates of 83.7%5 and 78.1%,6 respectively. In recent reports, however, SARS-CoV-2 variants of concerns (VOCs) have posted great challenges for vaccine induced protection (Wang *et al*.,2021; Kuhlmann *et al*.,2021).

The host immune response to SARS-CoV-2 appears to play a critical role in disease pathogenesis and clinical manifestations. SARS-CoV-2 not only activates antiviral immune responses, but can also activiate uncontrolled inflammatory responses characterized by marked pro-inflammatory cytokine release in patients with severe covid-19 leading to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities. These SARS-CoV-2-induced immune abnormalities result in other microbial infection, septic shock, and severe multiple organ dysfunction. Therefore, mechanisms underlying immune abnormalities in patients with COVID-19 must be elucidated to guide clinical management of the disease (Yang *et al*., 2020; Zafer *et al*.,2021).

When vaccines are delivered into the human body, the immune system recognizes the antigens of microorganisms and produces antibodies against them, triggering a robust immunological reaction. This stops disease progression by stopping the pathogen from replicating after infection. As a result, vaccine research is critical for controlling the spread of SARS-CoV-2 infection and for lowering COVID-19 morbidity and death (DeSisto *et al*., 2021).

Vaccines that stimulate an immune response against the spike protein necessary for SARS-CoV-2 binding, fusion, and cell entry. As a result, vaccination causes anti-S and anti-RBD binding and neutralizing antibodies to be produced in the blood, but not anti-N antibodies. Vaccines cause early synthesis of serum IgA, IgM, and IgG antibodies, similar to infection (Wang *et al*,. 2021; Wisnewski, *et al*.,2021). as well as long-lasting memory B- and T- cell responses (Barouch *et al*., 2021; Sokal *et al*.,2021).

Longer-term components of the humoral response, such as memory B cells (Barouch *et al*., 2021; Sokal *et al*., 2021). support the protective effect of vaccine-induced immunity, just as they do with infection; vaccine-induced

CD4+ and CD8+ T cells remain relatively stable up to 6–8 months after vaccination (Barouch *et al*., 2021).

The IL-12, IL-15 and IFN- γ are essential drivers of inflammation and innate immunity, and they play a critical role in the formation and maintenance of adaptive immunity in response to infection and vaccination. Identification of a reliable cytokine induction signature that leads to effective vaccination would be critical for vaccine development and improvement (Fourati *et al*., 2019; Arunachalam *et al*., 2020).

Previous research has shown that the BNT162b2 mRNA COVID-19 vaccine elicits a variety of responses, but the mechanisms governing the quality and amount of these responses remain mostly unknown (Teijaro and Farber, 2021).

Another study found that administering the BNT162b2 mRNA vaccination resulted in a systemic cytokine/chemokine profile that included IL-15and IFN- γ all of which are important in activating innate immune responses, moulding adaptive immunity, and leading to immunological memory. Changes in IFN- γ and IL-15 levels were shown to be favorably linked with antibody titers against SARS-CoV-2 Spike-RBD (Bergamaschi *et al*., 2021).

The Aim of Study:

The aim of this study is to evaluate the immune aspects in people who vaccinated with corona vaccine compared to unvaccinated people with corona vaccine through the following objectives:

1-Evaluate the immune aspects IgG, IgM in peoples who were vaccinated with covid-19 vaccine with Vidas test and Rapid test compared to unvaccinated people with covid-19 vaccine.

2- Detect of some cytokines as IL-15,IL-12,and Interferon-gamma in vaccinated and unvaccinated people with covid-19 vaccine use ELISA in Babylon Iraq.

Chapter two

Literature Review

2. 1.Coronavirus (CoVs):

2.1.1. Definition of Coronaviruses:

Coronavirus (CoV) is a vast family of single-stranded, positive-sense RNA viruses in the Nidovirales order. The Roniviridae, Arteriviridae, and Coronaviridae families make up the order (Fehr and Perlman , 2015). The Coronaviridae family is split into two subfamilies: Torovirinae and Orthocoronavirinae (Fehr and Perlman, 2015).

The Orthocoronavirinae family is further divided into alpha-, beta-, gamma-, and delta-COVs (Fehr and Perlman, 2015). The taxonomy of these viral subtypes is based on phylogenetic grouping. Their viral RNA genome is about 26 and 32 kilobases long they may be isolated from a variety of animals. Birds, cattle, and animals including camels, bats, masked palm civets, mice, dogs, and cats are among them (Lu *et al*., 2020).

The COV is a significant pathogen due to its extensive distribution and infectivity, CoV pathogenic subtypes in humans are linked to minor clinical signs. The two major exceptions are the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). MERS-CoV was initially discovered in Saudi Arabia in 2012. It was found to be responsible for 2,494 confirmed cases, including 858 deaths (Lu *et al*., 2020).

A variant of the beta-COV quickly spread over Guangdong, China, in 2002. In 37 countries, this outbreak led in 8,000 illnesses and 774 deaths (Lu *et al*., 2020). In Wuhan, China, the epidemic in 2020 manifested as pneumonia of undetermined cause. A novel strain of COV has been identified as the cause by deep sequencing research and lab tests (Chen *et al*.,2020).

This virus was first known as 2019-nCoV and the International Committee on Virus Taxonomy of Viruses, on the other hand, identified it as the SARS-CoV-2 virus (Cascella *et al*., 2022).

The World Health Organization (WHO) named the sickness caused by this unique virus coronavirus disease-2019 on February 11, 2020. (COVID-19). The appearance and epidemics of CoVs on a regular basis signal a public health danger. This shows that newly developing CoVs might be transmitted from animal to human and human to human. Future outbreaks of such illnesses are increasingly likely due to continuous changes in ecology and environment (Chen *et al*., 2020).

2.1.2. History of Coronavirus Outbreaks:

Coronaviruses have evolved several times during the last 1000 years (Forni *et al*., 2017). The first coronaviruses were discovered through animal sickness, followed by the isolation of infectious bronchitis virus (IBV) from chickens in 1937 (Beaudette, 1937) and murine hepatitis viruses (MHV) from mice in 1949(Wang *et al*.,1990).

In 1946, atransmissible gastroenteritis virus (TGEV) was discovered in pigs in the United States (Bailey *et al*., 1949). Coronaviruses in humans were initially identified in the 1960s because of respiratory tract infections (Kahn and McIntosh ,2005). B814 and 229E were the first viruses to be isolated (Hamre and Procknow, 1966; Tyrrell and Bynoe, 1966).

Since then, numerous other coronavirus strains (OC16 and OC43) have been identified from people utilizing tissue culture (Tyrrell *et al*., 1975; McIntosh *et al*., 1967).

The number of coronaviruses discovered has continued to rise, now including viruses from calves, dogs, cats, bats, sparrows, rabbits, and turkeys (Siham and Enaam, 2020).

The SARS-CoV produced a disease outbreak in 29 countries in 2002–2003, with the majority of cases occurring in China and Hong Kong. Before the illness died out in part owing to rigorous quarantine practices, there were 8096 documented cases, of which 774 died, resulting in a 9.6% mortality rate. SARS-CoV appeared to be extremely closely linked to another virus from Himalayan palm civets, from which it may have evolved, based on the genome sequence (Guan *et al*., 2003).

Civets were later thought to be an intermediate host for SARS-CoV, with bats being the natural host (Luo *et al*., 2018).

In Yunnan province, China, undertook a five-year surveillance investigation of SARS-related coronaviruses isolated from horseshoe bats, finding SARS-like CoVs. In numerous genes, including S, ORF3, and ORF8, genome comparisons indicated considerable genetic variability among these viruses. Despite having different S protein sequences, all SARS-like CoVs may utilise the same human angiotensin-converting enzyme-2 (hACE2) receptor, indicating a tight link with SARS-CoV. SARS- CoV is thought to have originated via recombination of bat SARS-like CoVs before infecting civets, from which the recombinant virus spread to humans, triggering the SARS pandemic (Hu *et al*., 2017).

The MERS-CoV appeared ten years later in Middle Eastern nations, when it was transmitted to humans by dromedary camels (Zaki *et al.*, 2012). MERS-CoV has caused 2519 laboratory-confirmed illnesses and 866 fatalities (34.3 percent mortality rate) as of January 2020, with more than 80% of cases reported from Saudi Arabia (WHO, 2003). The MERS-CoV strains from

humans and camels are almost identical, with mutations (substitutions) in the S, ORF3, and ORF4b genes (Chu *et al.*, 2018). MERS-CoV is phylogenetically related to the HKU4 and HKU5 bat coronaviruses (Lau *et al*., 2013).

The MERS-CoV may have evolved in bats as a consequence of recombination events within the ORF1ab and S genes, according to a comprehensive examination of evolutionary connections (Dudas and Rambaut, 2016; Wang *et al*., 2015). MERS-CoV employs the human dipeptidyl peptidase 4 (DPP4) receptor to gain entry to the cell (Raj *et al*., 2013). This is also true for MERS-related CoVs isolated from bats in China, whose spike proteins can bind to the same receptor as MERS-CoV, indicating that MERS-CoV may have a bat origin (Luo *et al*., 2018).

2.1.3. Coronavirus Classification and Structure:

Coronaviruses are classified into four classes. Coronaviruses (CoVs) are spherical and around 125 nm in diameter, with club-shaped spikes extending from the virus's surface, giving the appearance of a solar corona, therefore the name coronaviruses. Helically symmetrical nucleocapsids are found within the envelope, which is unusual among positive-sense RNA viruses. CoVs belong to the Nidovirales order, Coronaviridae family, and Orthocoronavirinae subfamily (Fig. 2-1).

The CoVs have the biggest genomes among RNA viruses, with genome sizes ranging from 26 to 32 kilobases (kb). CoVs have been divided into four classes based on genetic and antigenic criteria: alphacoronavirus (α -CoV), betacoronavirus (b -CoV), gammacoronavirus (G -CoV), and deltacoronavirus (d-CoV). (van Regenmortel *et al*. 2000). SARS-Cov-2 has 79 percent homology with SARS-CoV and 50 percent with MERS-CoV,

according to next-generation sequencing. SARS-CoV-2 belongs to the subgenus Sarbecovirus of the genus Betacoronavirus, according to phylogenetic study.

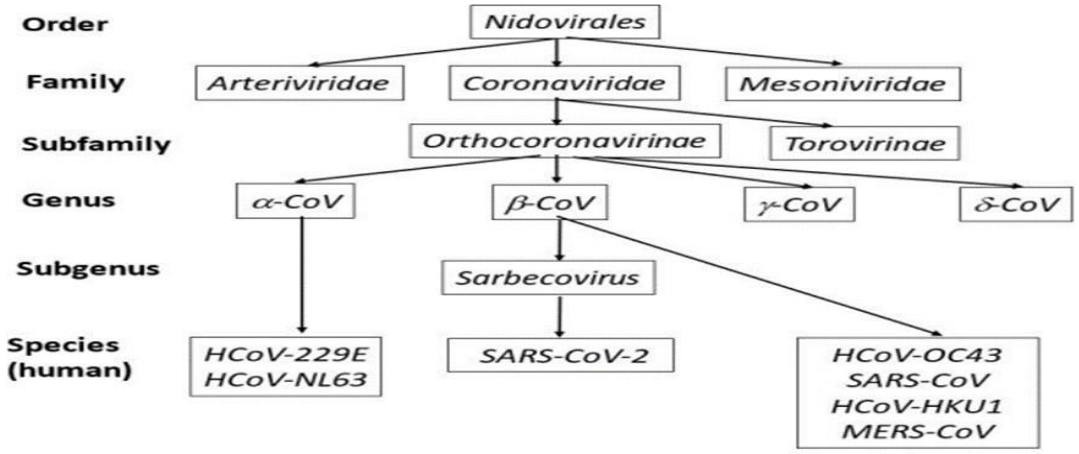


Figure (2-1) Classification of Human coronaviruses (**Neuman *et al*., 2006).**

2.1.4.Coronavirus Genomic Structure and Function:

The coronavirus genome is organized as follows: 5′ leader–UTR–replicase–S (Spike)–E (Envelope)–M (Membrane)–N (Nucleocapsid)–3′UTR–poly (A) tail, with auxiliary genes inserted between the structural genes at the 3′ end of the genome (Fig. 2-2).

FIG. 2: Genomes of SARS-CoV, MERS-CoV and SARS-CoV-2 (Li *et al*. 2020)[71]
Available from https://doi.org/10.1016/j.jpha.2020.03.001

Figure (2-2): Genome of SARS-CoV, MERS-CoV and SARS-CoV2 (**Fehr and Perlman, 2015).**

Most CoVs require the four structural proteins to generate a structurally complete viral particle, suggesting that certain CoVs may encode additional proteins with overlapping compensatory roles .While each key protein is essential in the formation of the viral particle, it is also engaged in other elements of the replication cycle. (Kuo and Masters, 2003; Song *et al*., 2004; Masters, 2006; Ruch and Machamer ,2012) .

The attachment of the virus to the host cell surface receptors, leading in fusion and subsequent viral entry, is mediated by the S protein (150 kDa) (Song *et al*., 2004; Kirchdoerfer *et al*., 2016).

The S protein also mediates cell-cell fusion between infected and nearby, uninfected cells in some CoVs, resulting in the creation of multinucleated giant cells, a method that permits direct viral propagation across cells while evading antibody neutralization (Qian *et al*., 2013).

The S protein is extensively N-linked glycosylated and uses an N-terminal signal sequence to obtain access to the endoplasmic reticulum (ER). The spike-like structure is made up of homotrimers of the virus-encoded S protein (Delmas and Laude, 1990).

The class I fusion protein is a trimeric S glycoprotein that facilitates binding to the host receptor and the S protein is split into two polypeptides, S1 and S2, by a host cell furin-like protease in most coronaviruses. (Fehr and Perlman, 2015) .S1 is the major receptor-binding domain of the S protein, while S2 is the spike's stalk. (De Groot *et al*.,1987; Zeng *et al.*, 2006).

The M protein (25–30 kDa) has three transmembrane domains and is the most abundant structural protein in the viral envelope.(Neuman *et al*., 2011;

Malik, 2020) .It features a short glycosylated ectodomain at the N-terminus and a considerably bigger endodomain at the C-terminus that extends 6–8 nm within the viral particle. (Nal *et al*., 2005).

The M protein exists as a dimer and may assume two alternative conformations, allowing it to increase membrane curvature and attach to the nucleocapsid, according to research. (Neuman *et al*., 2011).

The S-M protein interaction is essential for S retention in the ER-Golgi intermediate compartment (ERGIC)/ Golgi complex and integration into new virions, but not for the assembly process. (Fehr and Perlman, 2015).

Binding of M to N protein facilitates complete viral assembly by stabilizing the nucleocapsid (N protein-RNA complex) as well as the internal core of virions. (Escors *et al*.,2001).

The viral envelope is made up of M and E proteins, and their interaction is enough to produce and discharge virus-like particles (VLPs) (Liu *et al*., 2018).

The E protein is the smallest of the main structural proteins (8–12 kDa). This transmembrane protein has an ectodomain at the N-terminus and an endodomain at the C-terminus that possesses ion channel function. E is extensively produced inside the infected cell during the replication cycle, but only a tiny fraction of it is integrated into the viral envelope (Venkatagopalan *et al.*, 2015) .

The bulk of the protein is involved in the assembly and budding of viruses (Nieto-Torres *et al*., 2011) . Recombinant CoVs lacking E have been demonstrated to have lower viral titres, slow viral maturation, or produce incompetent offspring, highlighting the relevance of the E protein in virus generation and maturation (Ortego *et al*.,2002) .

The only protein that binds to the RNA genome is N protein (de Haan and Rottier, 2005).

The protein has two domains: an N-terminal domain (NTD) and a C-terminal domain (CTD). It has been claimed that both of these domains are required for efficient RNA binding (Chang *et al*., 2006).

It is also involved in viral assembly and budding, which leads to virion production (Schoeman and Fielding, 2019).

2.2. Replication Cycle of the Coronavirus:

2.2.1. Attachment and Entry:

Interactions between the S protein and its receptor cause the virus to attach to the host cell. Each coronavirus has a different location for receptor binding domains (RBD) inside the S1 region of the S protein. The RBD is found at the N-terminus of MHV and at the C-terminus of SARSCoV (Cheng *et al.*, 2004) .

The interaction between the S-protein and the receptor is the most important factor in infecting a host species and controlling viral tissue tropism. Although many coronaviruses employ peptidases as their cellular receptor, SARS-CoV and HCoV-NL63 use angiotensin-converting enzyme 2 (ACE2). Following receptor engagement, the virus enters the cytoplasm of the host cell by cleaving the S protein with an acid-dependent protease such as cathepsin, TMPRRS2, or another protease, followed by fusing of the viral and cellular membranes. The RBD and fusion domains of the S protein are separated by the initial cleavage, which happens at two locations within the S2 part of the protein and the second (cleavage at S2′) to reveal the fusion peptide. After cleavage at S2′, a fusion peptide enters into the membrane, and two heptad repeats in S2 are joined to create an antiparallel six-helix bundle. The fusing and eventual

release of the viral genome into the cytoplasm occurs as a result of the development of this bundle(Belouzard *et al*., 2009; Socher et al.,2021).

2.2.2. Replicase Protein Expression:

The replicase gene is translated from the virion genomic RNA in the following phase of the coronavirus lifecycle. Coronaviruses have two or three proteases that break the polyproteins that make up the replicase (V'kovski *et al.*, 2021).

The replicase-transcriptase complex (RTC) then assembles many of the non-structural proteins (nsps) to produce an environment favorable for RNA synthesis, and is ultimately responsible for RNA replication and transcription of the sub-genomic RNAs. Other enzyme domains and activities are also found in the nsps.(Clayton *et al.*, 2021).

2.2.3. Replication and Transcription:

The translation and assembly of viral replicase complexes are followed by viral RNA synthesis. Both genomic and sub-genomic RNAs are produced by viral RNA synthesis. Sub-genomic RNAs function as messenger RNAs for the structural and auxiliary genes found downstream of the replicase polyproteins(Neuman *et al*., 2014).

The order Nidovirales is distinguished by the fact that all positive-sense sub-genomic RNAs are 3′ co-terminal with the full-length viral genome, forming a collection of nested RNAs. Negative-strand intermediates are used to make both genomic and sub-genomic RNAs. These negative-strand intermediates, which include both poly-uridylate and anti-leader sequences, are only approximately 1% as prevalent as their positive-strand counterparts. (Fehr and Perlman, 2015) .

Coronaviruses are also recognized for their propensity to recombine in both homologous and non-homologous ways (Lai *et al.*,1985).

Capacity of these viruses to recombine is contingent on the ability of the RNAdependent RNA polymerase to swap strands (RdRp). Targeted RNA recombination, a reverse genetics approach used to construct viral recombinants at the 3′ end of the genome, is based on recombination, which is anticipated to play a substantial role in viral evolution (Masters and Rottier, 2005).

2.2.4. Assembly and Release:

The S, E, and M proteins are translated and introduced into the endoplasmic reticulum (ER) after replication and subgenomic RNA production (Malik, 2020). These proteins make their way into the endoplasmic reticulum-Golgi intermediate compartment through the secretory route (ERGIC) (Krijnse *et al*.,1994).

The viral genomes encapsidated by the N protein will bud into the membrane in the compartment, culminating in the creation of the mature virus. (de Haan and Rottier, 2005).

Most of the proteinprotein interactions essential for coronavirus assembly are directed by the M protein. However, virus-like particles (VLPs) can only be generated when M and E proteins are both expressed, suggesting that these two proteins are required to make coronavirus envelope. (He *et al*., 2004).

Inducing membrane curvature and inhibiting M protein aggregation are two more functions of the E protein. Virions are assembled and transported to the cell surface in vesicles, where they are discharged by exocytosis(Fenrich *et al*., 2020).

Novel coronavirus strains will continue to evolve, emerge, and create new outbreaks due to their capacity to recombine, mutate, and infect a variety of species(Mohapatra and Menon, 2022).

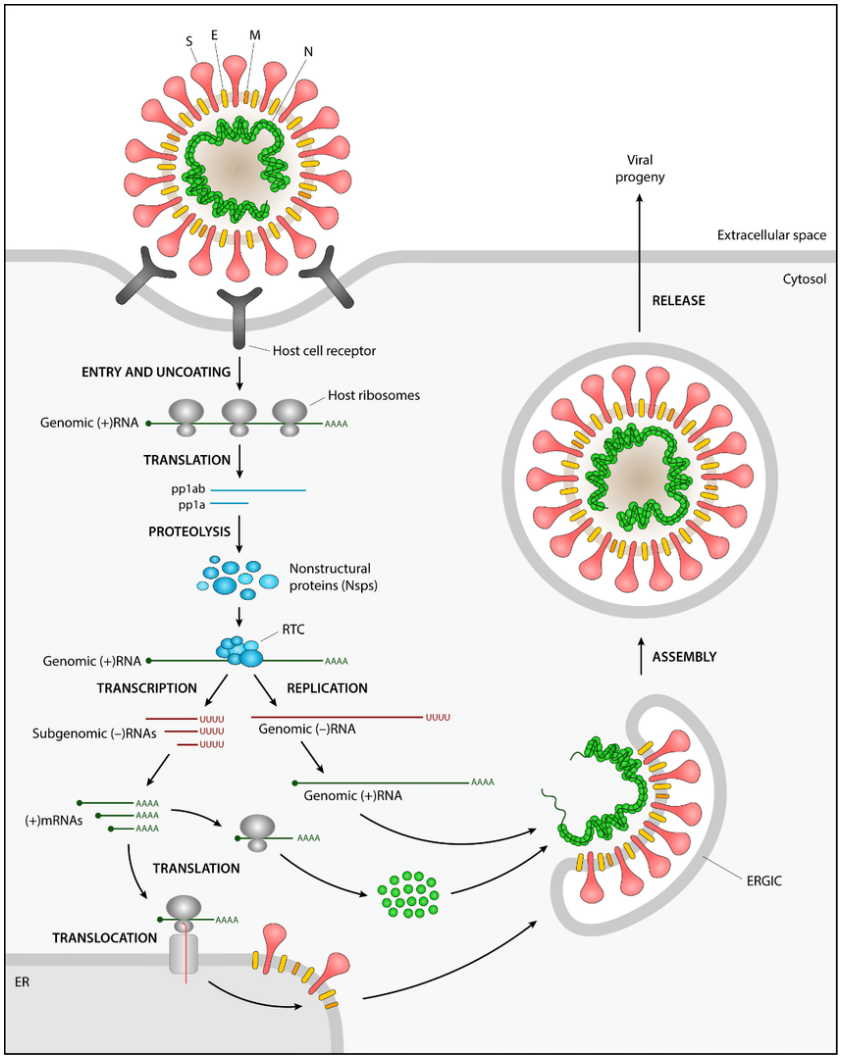


Figure (2-3): A typical coronavirus replication cycle. When the viral particle recognizes the host cell receptor, it enters the cell and uncoils,

releasing its positive-sense genomic RNA. Polyproteins pp1a and pp1ab are translated by host ribosomes and self-cleave to form nonstructural proteins (Nsps). Several Nsps form the replicase-transcriptase complex (RTC), which creates structural and accessory protein mRNAs as well as positive- sense genomic RNAs through transcription and replication. Smooth vesicles produced from the endoplasmic reticulum-Golgi intermediate compartment are used to build viral core particles (ERGIC). Exocytosis is the process through which the viral offspring is discharged **(**Llanes *et al*.,2020).

2.3.Mechanismsof human immune systems defenceagainstCOVID19:

Whoever there is no approved treatment for COVID-19, the immune system is the greatest line of defense because it helps the body's natural capacity to fight pathogens (such as viruses, bacteria, fungus, protozoa, and worms) and resist infections. COVID-19 infections go overlooked as long as the immune system is working correctly. Innate immunity (quick reaction), adaptive immunity (delayed response), and passive immunity are the three forms of immunity. Natural immunity, which comes from the mother, and artificial immunity, which comes from medicine, are the two forms of passive immunity. When the body is harmed, skin and inflammatory reactions occur (Chowdhury *et al*., 2020; Chegni *et al*., 2022).

When the body is exposed to germs or viruses for the first time, the immune system is unable to function correctly, and disease can result. This is exactly what happened in the instance of COVID-19 (Chaussabel *et al*.,2010).

When immune system cells have completed their education, they recirculate between central and peripheral lymphoid organs and migrate to and from injury sites through blood. Blood works as a conduit for the immune system, transporting naive and trained immune cells from one spot to another as it circulates throughout the body. After departing these nodes via outgoing lymphatic channels, the cells enter the circulation to be distributed to tissues throughout the body (Chowdhury *et al*., 2020; Alon *et al*., 2021).

For the study of the human immune system, several molecular and cellular profiling tests are currently accessible (Fig. 2-4). Instruments have progressed to a higher level of sophistication (e.g., polychromatic flow cytometers have improved). Major technical advancements have also happened in the disciplines of genomes and proteomics, resulting in a unique capability for the study of human beings in health and illness, where intrinsic

heterogeneity necessitates the analysis of vast collections of samples (Foster *et al*., 2007; Chowdhury *et al*., 2020).

Immune responses to viral infection mediate antibody production T cells help B cells develop into plasma cells, which generate antibodies that are specific to a viral antigen (Dörner and Radbruch, 2007).

A neutralizing nature antibody is effective in entirely inhibiting the virus from entering host cells, limiting infection, and playing a critical protective function later in infection, preventing infection recurrence. Infected cells, on the other hand, show a cellular immune response, which is mediated by T-lymphocytes. Helper T cells are in charge of the entire adaptive immune response, while cytotoxic T cells are essential for the clearing and cleansing of virally infected cells (Lu *et al*., 2018).

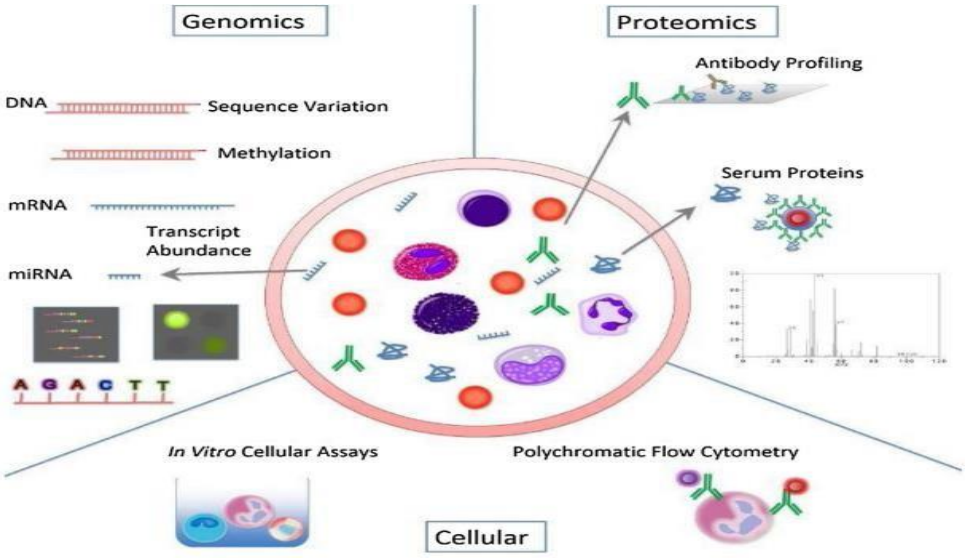


Figure (2-4): Armamentarium for immune profiling (Chowdhury *et al*., 2020).

2.4.Humoral Immune Response to covid-19:

Antibody testing look for antibodies generated by B cells against a particular infection. (Gronvall *et al.*, 2020). Antigen-presenting cells induce the activation and differentiation of B cells into antibody-secreting plasma cells (e.g., dendritic cells, macrophages, helper T cells). In response to infection, the body creates two kinds of antibodies: immunoglobulin M (IgM) and immunoglobulin G (IgG). IgM antibodies are created shortly after infection, whereas IgG antibodies are produced later to keep the body's immune system in check. (Gronvall *et al*., 2020; Ghaffari *et al*., 2020). IgA, the third kind of immunoglobulin, is present on mucous membranes and helps the innate immune system(Ghaffari *et al*., 2020).

Antibodies against SARS-CoV-2 virus particles form between 6 and 10 days after infection, peak at 12 days, and last for 35 days, according to current clinical findings. IgG antibodies, on the other hand, peak at 17 days and can last up to 49 days . Immunoglobulins generated in the presence of antigens from SARS-CoV-2 are detected by serological or antibody testing(Ghaffari *et al*., 2020; Tang *et al* .,2020; Legros *et al*., 2021).

2.4.1.Antibody Tests for Detecting COVID-19 Antibodies:

Antibody tests, which use lateral flow assays to identify antigens (spike, membrane, or nucleocapsid proteins) or antibodies for COVID-19, are a quick way to find out(Sullivan *et al.*, 2020) . Rapid diagnostic tests (RDT), enzyme-linked immunosorbent assays (ELISA), neutralization assays, and chemiluminescent immunoassays are the four main types of antibody testing, as illustrated in Table(2-1) (Gronvall *et al*., 2020).

According to current World Health Organization standards, a blood sample should be taken during the first week of sickness and then again three to four weeks later to test for SARS-CoV-2 antibodies (Yan *et al*., 2020).

In COVID-19 patients, the IgM positive rate climbed from 50% to 81 percent within 5 days of infection, while the IgG positive rate went from 81 percent to 100%.Unlike nasopharyngeal RT-PCR studies, antibody tests allow for improved epidemiological data collecting, evaluation of asymptomatic people' immunological state, and screening for past exposure. (Sullivan *et al.*, 2020).

Table (2-1) Covid-19 Antibody Test Types*

Type of test	Time to results	Antibodies
Rapid diagnostic test	10–30 minutes	IgG and IgM
Enzyme-linked immunosorbent assay	2–5 hours	IgG and IgM
Neutralization assay	3–5 days	N/A
Chemiluminescent immunoassay	1–2 hours	IgG, IgM, and IgA

*

Source: The Johns Hopkins Center for Health. (Gronvall *et al*., 2020).

Antibody tests are ineffective for detecting COVID-19 after the first week of symptoms and should be used no later than two weeks after the onset of symptoms. The overall duration of IgG, IgM, and IgA antibodies after COVID-

19 infection is unknown. As a result, it's unknown if antibody testing in the general population can detect early COVID-19 infections (Sotgiu *et al*., 2020).

Most antibody tests have been performed on hospitalized people with higher COVID-19 antibody titers. It's unclear if asymptomatic persons or those with a mild form of COVID-19 who have lower antibody titers can be examined with the same antibodies (Joyner *et al*., 2020).

The sensitivity of antibody testing has also been questioned in connection to the development of COVID-19 symptoms due to differences in how they are delivered. (Herd *et al*., 2001).

Comparing antibody tests to COVID-19 RT-PCR findings in nonexposed persons, as well as people with asymptomatic, moderate, and severe COVID-19, requires more investigation(Kuwelker *et al*., 2020) .

2.5.Covid-19 and cytokines:

Cytokines are a group of polypeptide signaling molecules responsible for regulating a large number of biological processes via cell surface receptors. Key cytokines include those involved in adaptive immunity (e.g., IL-2 and IL-4), proinflammatory cytokines and interleukins (ILs) (e.g., interferon (IFN) , IL-1, IL-6, IL-17 and TNF-α) and anti-inflammatory cytokines (e.g., IL-10). In response to stress-generating internal processes (e.g., cancer or microbial infection) host cells secrete cytokines with a highly important role in cell metabolism reprogramming as a defensive response (O'Neill, 2015; Vabret *et al*., 2020).

Metabolic dysfunctions caused by viral infection requires a reprograming of the host metabolism to generate effective antiviral defense responses. Data published on interferences between the actions of viruses and cytokines reveal

the molecular mechanisms underlying the innate immune response against viral infection (Agalioti *et al*., 2000).

The SARS-CoV-2 and cytokines The immediate immune response to infection by viruses, bacteria, or other microorganisms involves the mobilization of cells and molecules and draws on energetic, enzymatic, and biosynthetic resources; i.e., metabolic resources (Bambouskova *et al*. ,2018) inappropriate and weak immune response‖ appears more frequently in patients with comorbidities. Thus, this could favor virus replication and enhance complications related to severe cases of the disease (Blanco-Melo *et al*., 2020; Pirabe *et al*., 2021).

The key point in SARS-CoV-2 infection could be the depletion of antiviral defenses related to innate immune response as well as an elevated production of inflammatory cytokines, individuals with comorbidities are more likely to have a "inappropriate and inadequate immune response." As a result, this might encourage viral replication and exacerbate difficulties associated with severe illness cases) The depletion of antiviral defenses associated to the innate immune response, as well as an increased generation of inflammatory cytokines, may be the critical point in SARS-CoV-2 infection (Blanco-Melo *et al*., 2020).

Cytokines and SARS-CoV-2 The rapid immunological response to infection by viruses, bacteria, or other microbes necessitates the mobilization of cells and molecules, as well as the utilization of energetic, enzymatic, and biosynthetic resources; in other words, metabolic resources (Bambouskova *et al*., 2018).To create efficient antiviral defensive responses, metabolic dysfunctions induced by viral infection necessitate a reprogramming of the host metabolism. Interactions between the effects of viruses and cytokines have been documented, revealing the molecular processes underpinning the innate immune response to viral infection (Agalioti *et al*., 2000).

2.5.1.Interleukin-12:

Interleukin-12 belongs to a class of heterodimeric proteins with specific properties, such as pairing veracity (also seen in IL-23, IL-27, and IL-35), that are engaged in molecular processes and activities and play a key role in positive and negative feedback (Jones and Vignali, 2011).

Dendritic cells, macrophages, neutrophils, and human B-lymphoblastoid cells (NC-37) all naturally release interleukin 12 (IL-12) in response to antigenic stimulation (Kaliński *et al*., 1997).

The IL-12 family, which comprises IL-12, IL-23, IL-27, and IL-35, is remarkable in that it contains the only heterodimeric cytokines. Despite having numerous structural similarities and molecular partners in common, they mediate a wide range of functional consequences (Vignali and Kuchroo, 2012) .

The development of naïve T cells into Th1 cells is aided by IL-12. (Hsieh *et al*., 1993).

It is called a T cell-stimulating factor because it can help T cells grow and operate, T cells and natural killer (NK) cells produce more interferon-gamma (IFN-) and tumor necrosis factor-alpha (TNF-), and IL-4-mediated inhibition of IFN- is reduced. CD30, a coreceptor related with IL-12 activity, is found on T cells that generate IL-12 (Mal and Trinchieri, 2001).

This cytokine's impact in viral infections stems from its direct chemotactic effects on NK cell infiltration, which increases their binding to vascular endothelial cells. IFN- is secreted by NK cells, which acts as a positive feedback loop by boosting the production of IL-12 (Komastu *et al* .,1998).

The IL-12 gene expression is rapidly induced by viral infections, and it also functions after viral replication (Kanangat *et al*., 1996).

Patients infected with SARS-CoV- as well as those infected with other coronaviruses such as SARS-CoV have shown elevated blood IL-12 levels (Zhou *et al*., 2020; Huang *et al*., 2020).

For example, IL-12 is generated endogenously during influenza pneumonia and stimulates NK cells, which release IFN- and so suppress viral multiplication. CD8 + T cell responses have been reported to enhance when IL-12 is used (Komastu *et al.*,1998).

The MSCs have been recommended as an effective treatment against COVID-19 because they decrease the release of IL-12, as well as IFN- and TNF- (Zhang *et al*., 2014).

2.5.2.Interleukin-15:

Interleukin -15 is a glycoprotein that belongs to the four-helix bundle cytokine family (Perera, 2001). Cellular IL-15 production appears to be tightly regulated in both humans and mice via transcription, translation, translocation, and intracellular trafficking (Waldmann and Tagaya, 1999).

Monocytes, macrophages, DCs, keratinocytes, epidermal skin cells, fibroblasts, various epithelial cells, bone marrow stromal cells, and nerve cells are among the cell types that produce IL-15 mRNA constitutively furthermore, IL-15mRNA is found in the kidney, placenta, lung, heart, skeletal muscle, and brain. Despite the widespread expression of IL-15 mRNA, very few other cells and tissues secrete detectable levels of IL-15 proteins, with the exception of monocytes, DCs, epithelial cells, bone marrow stromal cells, and fibroblasts (Di Sabatino *et al*., 2011).

The IL-15 provides survival signals that keep memory T cells alive in the absence of antigen and has also been linked to the formation of NK cells and have inhibits apoptosis in rodent lymphocytes by increasing BCL2L1/BCL-x(L), an apoptosis inhibitor(Malamut *et al.*, 2010).

The IL-15 receptor shares certain subunits with the receptor for Interleukin 2 (IL-2) a structurally similar cytokine, allowing the two cytokines to compete for and adversely regulate each other's activity balance between IL-15 and IL-2 regulates the amount of CD8+ memory T cells. JAK kinase, STAT3, STAT5, and STAT6 transcription factors are activated when IL-15 binds to its receptor, eliciting downstream signaling processes(Harwood and O'Connor, 2021).

In response to various exercise doses (myokine), skeletal muscle produces IL-15 and its receptor subunit alpha (IL-15R), which play important roles in visceral (intra-abdominal or interstitial) fat reduction and myofibrillar protein synthesis (hypertrophy) (Pedersen, 2011).

2.5.3.Interferon Gamma:

The IFN-γ is a type produced by a wide variety of lymphocyte cells, including CD4+ and CD8+ T cells, Treg cells, FoxP3+ CD8− T cells, B cells, and NK cells. Monocytes, macrophages, dendritic cells, and neutrophil granulocytes can also produce this cytokine. Although numerous cells can be the source of IFN-γ, it is mainly produced by T and NK cells. MSCs can also secrete low IFN-γ levels to regulate hematopoiesis (Tang *et al*., 2018).

The IFN-γ participates in numerous immune and adaptive immunological functions and in inflammatory processes. It promotes macrophage activation and antigen presentation and is highly involved in anti-bacteria and anti-virus

immunity and in signal transduction. It is difficult to classify IFN-γ as a pro- or anti-inflammatory cytokine, given its complex and varied roles (Lees, 2015; Huang *et al*.,2020).

Found that serum IFN-γ levels were higher in patients with COVID-19 than in healthy individuals and proposed that the elevation of this and other cytokines might result from the activation of Th1 and Th2 cells. Also, elevated serum IFN-γ levels were previously reported in patients with SARS- CoV or MERS (Belghith *et al*., 2018; Liu *et al*., 2020).

Observed that elevated IFN-γ levels were associated with greater viral load and lung damage (Liu *et al*., 2020; Sun et al. 2020).

Found that IFN-γ, IL-6, and IL-10 levels were higher in patients with infection by SARS-CoV-2 but did not differ between patients who required ICU admission and those who did not. In fact, these authors found that levels of this cytokine were lower in CD4+ T-cells from patients with severe versus mild symptoms and suggested that the infection may initially affect CD4+ and CD8+ T-cells, reducing the production of IFN-γ (Ren *et al*., 2021).

2.6. Covid-19 Vaccine:

The emergence and spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic with over 3.8 million deaths1 and rapid development of multiple vaccine candidates (Dong *et al*.,2020).

The SARS-CoV-2 infection elicits antibodies against spike protein (S) and nucleoprotein (N)(Okba *et al*.,2020). of which, on the basis of virus challenge studies in animals, the spike protein-specific antibodies are neutralizing and associated with protective immunity (Deng *et al*.,2020).

In addition, recent studies of COVID-19 patients and vaccinees indicate that previous infections and vaccinations are related to a decreased rate of SARS-CoV-2 infections (Hanrath *et al*.,2021).

Although the persistence of vaccine induced antibodies is still not known, infection-induced neutralizing antibodies have remained detectable for at least six months after symptom onset (Pradenas *et al*.,2021).

Vaccines may enhance the immune system to fight against the viruses and help an individual to prevent the infection of the pandemic, and, thus, many governments in the world are trying their full efforts to obtain sufficient vaccine supplies and speed up vaccination for the public. Currently, European, European Medicines Agency (EMA) has authorized four vaccines to be used in European Union: two mRNA vaccines (BNT162b2/Comirnaty by Pfizer-BioNTech and mRNA-1273 by Moderna) and two adenoviral vector-based vaccines (ChAdOx1-S by AstraZeneca-Oxford and COVID-19 Vaccine Janssen by Janssen Biologics B.V. and Janssen Pharmaceutica NV)(Mascellino et al.,2021; Wu et al.,2021).

Vaccination can provide direct protection for the vaccinated individual to resist the attack of the virus and is a healthy way to limit the transmission of the pandemic through gaining population immunity (Wheelock, 1965).

2.6.1. Development of Coronavirus Vaccines:

Various monoclonal antibodies (mAbs) against SARS-CoV were released one after the other during the SARS pandemic. The mAbs were employed in diagnosing, treating patients, and doing fundamental research (Kato *et al*.,2019).

Although mAbs generated antiviral effects in MERS-CoV infection cases based on cell cultures and animal models, the treatment window for mAbs is generally small, and large-scale manufacture requires a long time and a lot of money, which restricts their use in high-risk MERS-CoV locations. The best protection against MERS-CoV is currently vaccination.(Xu *et al*., 2019).

The S glycoprotein containing an RBD has become the key focus for MERS-CoV immunogen selection and vaccine design due to its essential involvement in viral entry and as a major target for NAbs. (Xu *et al.*, 2019). We now know that SARS-S CoV's protein binds to the cell receptor ACE2, which identifies the S protein at amino acid residues 318–510 (aa318–510) (Li *et al*., 2003) and MERS-cell CoV's receptor is DPP4 (also known as CD26) RBDs are the names given to these areas (Raj et al., 2013).

As a result, NAb reactions are primarily directed towards the S protein, particularly its RBD. Simultaneously, same goals are being used in the development of SARS-CoV vaccines (Du *et al*., 2009) . According to reports, intramuscular (i.m.) inoculation of mice with an RBD-based vaccine gives long-term resistance to SARS-CoV infection (Du *et al*., 2007) .

Some progress has been achieved in the study and development of CoV vaccines in recent years. Over 20 vaccine candidates have been published using various approaches, including DNA vaccines, recombinant protein components, recombinant viral vectors, virus-like particle vaccines VLP-based CoV vaccinations are safe and well-tolerated. (Mohsen *et al*., 2017).

TheVLPs are made up of one or more protein subunits that the immune system may quickly detect. Furthermore, the highly structured protein particles produced by the virus's single or many structural proteins preserve the viral antigen protein's original shape, activating the host's innate and adaptive immune response. (Mohsen *et al*., 2017).

The VLP vaccine can induce specific IgG antibodies targeting the MERS-CoV RBD, with the endpoint titer reaching as high as 1:1,280. MERS-CoV-like particles created by the baculovirus expression system are structurally similar to the natural virus (Wang *et al*., 2017).

2.6.2. Live Attenuated and Inactivated Vaccines:

Full-length recombinant S proteins have been shown to be highly immunogenic and capable of eliciting a potent protective immune response.(Zhou *et al*., 2006).

Antibody responses can be improved by utilizing adjuvant combinations with customized subunit rebuilding. (Lan *et al*., 2014) The S1 subunit, particularly the RBD, has been identified as a key target for NAbs in mice, NHPs, and humans in studies of SARS-CoV vaccines(Tao *et al*., 2016).

The MVA virus,adenovirus,and measles virus are examples of viral vectored vaccines that have the capacity to elicit robust humoral and cellular immune

responses (MV). The MVA-based, full-length S MERS-CoV vaccine (MVA-S) developed by the German Center for Infection Research is the most promising contender for MERS-CoV (Volz *et al*., 2015).

The MVA-S is enough to elicit strong NAb responses in mice and inhibit viral replication in the lower respiratory tract(Volz *et al*., 2015) . Human adenovirus Type 5 or 41 vector-based vaccines containing the MERS-CoV S protein have been shown to produce antigen-specific IgG and NAbs in blood (Guo *et al*., 2015) .

In hamsters, mice, ferrets, and NHPs, vaccines based on chemically inactivated SARS-CoV particles were tested. NAbs produce various amounts of protective immunity in these animal models (Bolles *et al*., 2011).

According to a research, SARS-CoV can cause Th2 immunopathological alterations in mice, implying that SARS-CoV components might cause hypersensitive responses. Further research has revealed that viral nucleoproteins have a role in the immunopathology that leads to eosinophilia(Bolles *et al*., 2011).

Furthermore, after a viral assault, oligomeric vaccination with the SARS-CoV S protein causes an increase in eosinophils in many animal model systems (Tseng *et al*., 2012).

The mRNA vaccines have a number of advantages, including good immunogenicity, a fast research and development cycle, and the ability to prevent infectious illnesses. The industry considers it to have breakthrough potential. The platform for developing gene vaccines has been validated in terms of immunogenicity and vaccination efficacy in recent years. (Almazán *et al*., 2013).

All these vaccines aim to generate spike protein-specific antibodies and all have been shown to induce anti-S IgG antibodies with neutralizing activity against the first pandemic SARS-CoV-2 (Folegatti *et al*.,2020).

2.7.Types of Covid-19 Vaccines:

2.7.1.Astrazenca:

Adenovirus-vectored experimental vaccination for chimpanzees against SARS-CoV-2 glycoprotein spikes has been produced by AstraZeneca and Oxford University. Nonhuman primates were administered a prime-boost vaccination regimen (viral particles in each dose at a concentration of (2*5 1010), and the vaccine displayed both immunogenicity and defensive effectiveness (van Doremalen *et al*., 2020). persons were administered the vaccine and were given a primate protocol (viral particles in concentration 5•0101) and a prime-boost schedule (2•5 1010 or 5•0 1010 viral particles) in a 1/2 phase trial. Following the first dose of vaccine, some recipients exhibited antibody responses, including neutralizing antibodies and anti-spike glycoprotein IgG, as well as an IFN T-cell response, and humoral immunological outcomes improved with the second dose of vaccine (Folegatti *et al.*, 2020).

2.7.1. Moderna Company Vaccine:

Moderna's vaccine, also known as (mRNA-1273), is a nucleoside-modified messenger RNA vaccine that encodes a membraneanchored, full-length SARS-CoV-2 spike (S) protein with two-point mutation proline substitutions that selectively lock the protein in an antigenic prefusion

conformation. This mRNA is contained in a lipid nanoparticle formulation that permits it to be taken up and translated into the viral S protein by host cells. After that, the S protein binds to the cell membrane, triggering an adaptive immune response that includes both B-cell-mediated neutralizing antibodies and antigen-specific T-cell immunity (FDA, 2020) .

The vaccine is delivered in a two-shot series of 100-g doses, each given 28 days apart as intramuscular (IM) injections. The cell-free production procedure, which has been used in the creation of mRNA vaccines for ten years, is free of vectors, animal products, adjuvants, and preservatives (Zhu *et al* ., 2020).

2.7.2. Pfizer and BioNtech :

The COVID-19 vaccines based on mRNA have also been developed by Pfizer and BioNtech. The Pfizer/BioNtech vaccine is administered by lipid nanoparticles with phospholipid membranes around the mRNA that codes for the COVID-19 virus's S protein (Cross, 2021).

The phospholipid membrane of the lipid nanoparticle will fuse with the host membrane after injection, releasing the mRNA into the cytoplasm of the target cell. The S protein's mRNA is subsequently translated in the rough endoplasmic reticulum, resulting in the S protein being produced in the cytoplasm (Hall *et al*.,2022).

Major Histocompatibility Complex I (MHC I) and II breakdown the S protein and express it (MHC II). Antigen-presenting immune cells such as macrophages, dendritic cells, and B-cells include MHC II. With its TCR protein, a T-helper cell attaches to the S protein fragment provided by the MHC II molecule, as well as the MHC II molecule itself with its CD4 receptor.

Interleukins are subsequently released by the T- Helper cell, causing B cells to proliferate and develop into plasma cells. Specific antibodies to the S protein fragment are then released by these plasma cells. The initial T-Helper proliferates and forms T- Helper memory cells as a result of these interleukins (De Soto, 2021).

By attaching to S protein fragments produced by non-immune cells via the MHC I complex, cytotoxic T cells play a role. The cytotoxic T cell's CD8 molecule will attach to MHC I, whereas the TCR of the cytotoxic T cell will bind to the S protein fragment. The cytotoxic T cell will subsequently release cytokines, enhancing the T-Helper cell's own promotion of B cell differentiation into plasma cell proliferation. The cytotoxic T cell will also be prepared to attack any infected cells that subsequently present with the COVID19 virus's S protein(Rijkers *et al*., 2021).

Pfizer's lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine induces RBD-binding IgG and neutralizing antibodies with mainly mild side effects in 45 volunteers in a study comparing two types of vaccines (BNT162b1 and BNT162b2) (Mulligan *et al*., 2020) .

2.7.3. Sinopharm:

Sinopharm COVID-19 vaccine or BBIBP-CorV, an inactivated vaccine made by Beijing Bio-Institute of Biological Products, was the first Chinese COVID-19 vaccine that WHO approved for emergency use (BBIBP). Sinopharm was shown to be safe and well tolerated in the studies, with 100% of vaccinated people reporting a robust humoral immune response. Furthermore, animal trials on rats, mice, rabbits, and guinea pigs demonstrated that Sinopharm provided adequate protection against SARS-CoV-2 (Vickers, 2017).

The most common side effects of Sinopharm vaccine (with 79 percent efficacy against symptomatic COVID-19 and 79 percent efficacy against hospitalization) were dizziness, fatigue, headache, nausea, vomiting, fever, and allergic dermatitis, according to the WHO report on Sinopharm/ BBIBP COVID-19 vaccine (Ghiasi *et al*., 2021).

It was found that the most prevalent adverse responses were injection site discomfort and fever, both of which were moderate and self-limiting with no major side effects. Overall, the number of patients experiencing side effects was modest (Xia *et al*., 2020).

Fever is the most prevalent systemic adverse event, according to in another trial on BBIBP-CorV vaccination (18-59 years, 4% in the 2 and 4g group and 8% in the 8g group). Within 28 days after immunization, all reported adverse responses were mild or moderate, with no significant adverse events. On days 0 and 14, a two-shot vaccination with a three- or four-week delay produces stronger neutralizing antibody titers than a single 8- or 4-gram dose. It demonstrates that appropriate neutralizing antibody titers must be considered at suitable intervals (Hall *et al*., 2022).

Sinopharm has developed two inactivated whole-virus vaccines with alum adjuvant that are now being tested. The Wuhan Institution of Biological Products, a Wuhan-based research center in China, created the candidate for the first immunization (COVID-19- New Crown). The results of both phase 1 and phase 2 investigations are made available to the public. The stage 1 trial "number of volunteer 96" focused on a three-dose chain, while the stage 2 trial "number of volunteer 224" focused on a 5-g dose of vaccination in two groups, with the first dose given on days 0 and 14 with number of volunteer (n=84) & (n=28) respectively, and the second dose given on days 0 and 21 with number of volunteer (n=84) (n=28). The study's participants varied in age from 18 to 59

years old (Xia *et al*.,2020; Hadi et al.,2021). A second vaccine candidate created by the Beijing Institute of Biological Products is being studied by Sinopharm. A phase 3 experiment (with 5000 participants) is now ongoing in the United Arab Emirates (Deng *et al*., 2020).

2.7.4.Johnson and Johnson Vaccine:

The Ad26-SARS coronavirus vaccine, which expresses glycoprotein spikes in a replication-defective form (replication-defective vaccine), was evaluated in a phase 3 randomized, double-blind, placebo-controlled experiment with 60000 people aged 18 and above. A single inoculation with serotypes adenovirus type 26-vectored vaccine (1•0 1011 viral particles via the intramuscular route without adjuvant) generates robust neutralizing antibody responses in rhesus macaques aged 6–12 years, protecting them against SARS-Coronavirus 2 challenge (Corbett *et al*., 2020).

This potential vaccination, which must be kept between 2 and 8 degrees Celsius, was tested on 1045 people (18–55 and 65 years old) in a half-experiment in the United States and Belgium. The vaccine's safety profile and efficacy have yet to be made public by the company (Loftus *et al*., 2020; Hadi *et al*., 2021).

2.7.5.CanSino Biologics :

CanSino, a Chinese business, has developed a novel COVID-19 vaccine, an adenovirus recombinant serotype 5-vectored vaccine that produces the whole spike glycoprotein for SARS-CoV-2, also known as the Wuhan-Hu-1 viral strain. This vaccine candidate was examined by 108 adult volunteers ranging in age from 18 to 60 years old. in a phase 1 clinical study (Poland *et al*., 2020).

A single vaccination containing 5•0 1010 virus particles was administered to each participant. Neutralizing antibody titers against virus particles in concentrations of 10 1011 and 15 1011 rose from 31% to 50% on days 14 and 18 and on day 28, and the raised -dose group had improved from baseline at (75%) on day 28. The majority of side effects were mild, intermittent, and occurred within one week following vaccination, and included discomfort, fever, weariness, muscle or joint pain, as well as redness and swelling at the injection site (Wee and Simes, 2020).

2.7.6.Biotech Sinovac :

Biotech Sinovac is a coronavirus vaccine that was chemically inactivated, administered in two doses ((0-28 days)) and got an essential use authorisation from the CDC. Prior to the start of phase 3 trials in July 2020, Chinese officials will have supervision. According to accounts, this authorisation resulted in about 90% of the company's employees being inoculated. Healthy Participants in clinical trials 1/2 who were between the ages of 18 and 59 years old (Deng ,2020) .

The phase one investigation drew a total of 143 participants. 600 individuals were randomly assigned to receive either 3 g /0•5 mL or 6 g /0•5 mL of the experimental vaccination, or placebo, in two intramuscular injections on days 0 and 14, or day 0 and 28 (Zhang *et al* ., 2020).

Chapter Three

Materials and Methods

3.1 Materials and Methods:

3.1.1. Laboratory Instruments and Equipments:

All instruments used in the laboratory during the study were summarized in table (3-1).

Table (3-1): Laboratory Instruments and Equipment

No	Item	Company	Country
1	Centrifuge	Gemmy	Taiwan
2	Cloves	Latex	Chine
3	Cool box	Tank	India
4	Cylinder included	Latex	Iran
5	Cotton	Kardelen	China
6	Cylinder included	Latex	Iran
7	Chromate reader	Awarness technology	USA
8	Distillator	GFL	Germany
9	Deep freezer	Thermo-Fisher	Germany
10	Filter paper	ZELPA	Turkey
11	Gel tube	Afco	USA
12	Incubator	Memmert	Germany
13	Micropipette from 100-1000 µl	Dragon lab.	USA
14	Micropipette from 20-200 µl	Dragon lab.	USA
15	Micropipette from 5-50 µl	Dragon lab.	USA
16	Minividas	Biomerieux	France
17	Pipette tips (blue)	Applied Biosysyem	USA
18	Pipette tips (yellow)	Applied Biosysyem	USA
19	Panal tube (test tube)	LAB	China
20	Refrigerator	Vesti	Turkey
21	Rack	Bioneer	Korea
22	Syringe	SUPER	China
23	Sterile material (Ethanol)	Aljoud	Iraq
24	Tips (various volumes)	Applied Biosysyem	USA

3.1.2 Immunological and biological materials:

The immunological and biological materials were summarized in thefollowing table (3-2).

Table (3-2) List of Kits used in the study:

NO	Name	Company	Country
1	Human Interleukin-15	BT-LAB Bioassay Tech	China
2	Human Interleukin-12	BT-LAB Bioassay Tech	China
3	Human Interferon gamma	BT-LAB Bioassay Tech	China
4	SARS-COV-2 IgG Vidas	Biomerieux	France
5	SARS-COV -2 IgM Vidas	Biomerieux	France
6	SARS-COV -2 IgG Rapid Test	NIPIGN health CORP	Netherlands
7	SARS-COV-2 IgM Rapid Test	NIPGN health CORP	Netherlands

3.2.Subjects and Methods:

3.2.1 Participants:

The duration of sampling in the study was during the period from November/2021 to Jenuray/2022 on people vaccinated with the corona vaccine in AL Sadiq hospital,Hashymia hospital and different organ in Babylon city with two doses at different intervals after give the vaccine ranging from(2 W - 1Mom, 2 Mon - 3 Mon , 4 Mon - 5 Mon , > 5Mon)and were also collected from unvaccinated people as control include (Healthy and Cured) .The study was conducted on males and females whose ages range between 20 and more 60 years as study group who were diagnosed as vaccinated with the corona vaccine and the study was conducted on non infected and pre infected unvaccinated males and females as control.

3.2.2. Inclusion criteria

The people vaccinated with the corona vaccine were registered in the current study if it included the following criteria:

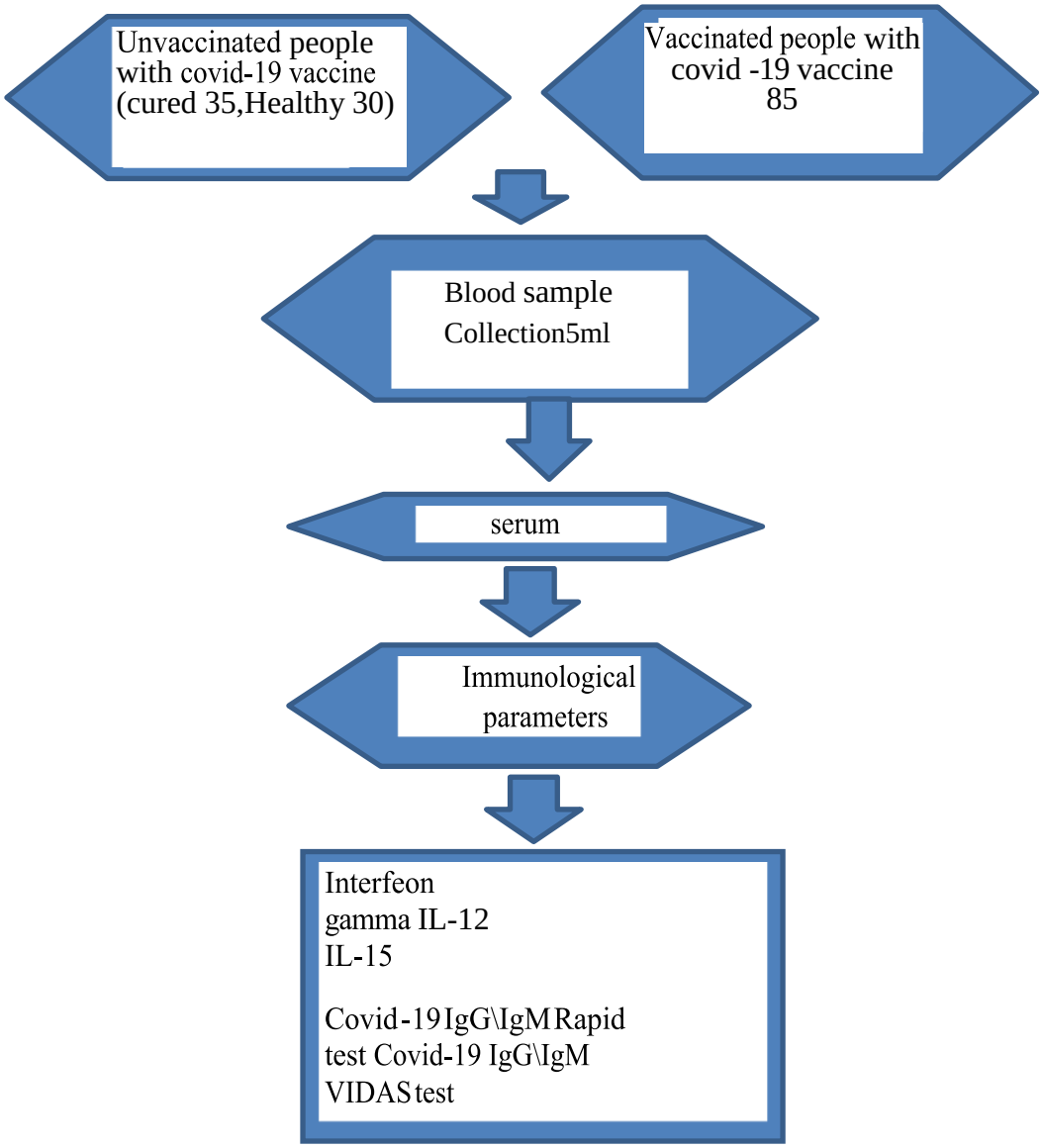
1. vaccinated people were confirmed through the vaccine card to know the full information included in the type of vaccine and they were vaccinated with two doses.

2. Participent must be free from any chronic disease.

3.2.3. Exclusion criteria:

People with chronic disease were excluded so that the vaccinated people who did not suffer from chronic disease were studied.

3.2.4. Study Design:



3.2.5. Sepcimens:

Five µl of venous blood was obtained from each participant. The blood was placed in gel tube and let to stand for 30 minutes, and then samples were centrifuge (3000rpm / 15 min). The serum collected divided into 3 Eppendorf (200 µl each) and kept in the freezer (-20 c) until it was used for the laboratory assays (Pazzagli *et al*., 2013).

3.2.6. Ethical approval:

The formal administrative agreements were obtained before data collection, which required for conducting the study as follows:

1. The initial agreement was obtained from the University of Babylon/ College of science for women / Higher education committee after protocol presentation.
2. The study protocol was accepted by an ethical committee of the Department of biology in University of Babylon / College of science for women.
3. A formal requisition was sent to the Babylon health Directorate for the agreement.
4. An official agreement was attained from the department of developing and training Babylon health Directorate.

3.4. Immunological Tests:

3.4.1. Covid-19 IgG\IgM Rapid Test:

The simple SAR-Cov-2 IgG/IgM product allows the detection of anti-SARS- Cov-2 IgG/IgM type antibodies generated by the immune system in response to the virus infection therefore its use is intended for the control of the immune response against the virus of people infected with the SARS-Cov-2 .

Assay procedure:

1-Is opened the container carefully take out the test strip.

2-Are transfered 10ml of serum into the loading area of the test strip. 3-Add 2 drops of diluent and leave it at ambient temperature.

4-Observe the result within 10-15 minutes and the interpretive result is invalid after 15 minutes.

5-Positive result; Both the quality control line line C and the detection line line G developed color indicating that a novel coronavirus IgG antibody was detected in the sample.

Both the quality control line line C and the detection line M developed color indicating that a novel coronavirus IgM antibody was detected in the sample. The quality control line C detection line G and line M all developed color indicating that both the novel coronavirus IgG antibody and the novel coronavirus IgM antibody were detected in the sample.

6-Negative result; only the quality control line C developed color.

7-Invalid, The quality control line C did not develop color.

3.4.2. COVID -19 IgG –IgM VIDAS TEST:

3.4.2.1.COVID -19 IgG VIDAS TEST:

The VIDAS SARS –COV-2IgG is an automated assay using the ELFA Enzyme Linked Fluorescent Assay technique intended for qualitative detection of IgG antibodies to SARS-Cov-2 in human serum or plasma lithum heparin on instruments of the VIDAS family.

assay principle:

Combines a tow step sandwish enzyme immunoassay method with a final fluorescence detection ELFA The single use

solid phase Receptacle SPR serves as the solid phase as well as the pipetting devise.Reagents for the assay are ready to use and pre dispensed in the sealed single use reagent strips. All of the assay steps are preformed automatically by the instrument.The reaction medium is cycled in and out of the SPR device several times.After the sample dilution step the SARS-Cov-2 IgG are captured by recombinant SARS-Cov-2 antigen coated into the interior of the SPR device wall. Unbound components are eliminated during washing steps. During the second step the IgG are specifically detected by anti-human IgG labeled with alkaline phosphatase. Unbound components are eliminated during washing steps. During the final detection step the substrate 4-Methyl-umbelliferyl phosphate is cycled in and out of the SPR device. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product 4-Methyl-umbelliferone the florescence of which is measured at 450 nm. At the end of the assay the results are automatically calculated by the instrument according to the S1 standard stored in memory and a test value is obtained. The results can then be printed out .

3.4.2.1. COVID -19 IgM Vidas Test:

The VIDAS SARS –COV-2IgM is an automated assay using the ELFA Enzyme Linked Fluorescent Assay technique intended for qualitative detection of IgM antibodies to SARS-Cov-2 in human serum or plasma lithium heparin on instruments of the VIDAS family.

assay principle:

Combines a tow step sandwich enzyme immunoassay method with a final fluorescence detection ELFA.

The single use solid phase Receptacle SPR serves as the solid phase as well as the pipetting devise. Reagents for the assay are ready to use and pre dispensed in the sealed single use reagent strips. All of the assay steps are preformed automatically by the instrument. medium is cycled in

and out of the SPR device several times. After the sample dilution step the SARS-Cov-2 IgM are captured by recombinant SARS-Cov-2 antigen coated into the interior of the SPR device wall. Unbound components are eliminated during washing steps. During the second step the IgM are specifically detected by anti-human IgM labeled with alkaline phosphatase unbound components are eliminated during washing steps. During the final detection step the substrate 4-Methyl-umbelliferyl phosphate is cycled in and out of the SPR device. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product 4-Methyl-umbelliferone the florescence of which is measured at 450 nm. At the end of the assay the results are automatically calculated by the instrument according to the S1 standard stored in memory and a test value is obtained. The results can then be printed out.

3.4.3. Cytokines Test:

3.4.3.1. Interleukin-15 (IL-15)

Assay Procedure

The immunosorbent assay linked to the enzyme ELISA test known IL-15 in the serum. The ELISA test is performed in the FIA is a following designed for the accurate quantitative detection of IL-15

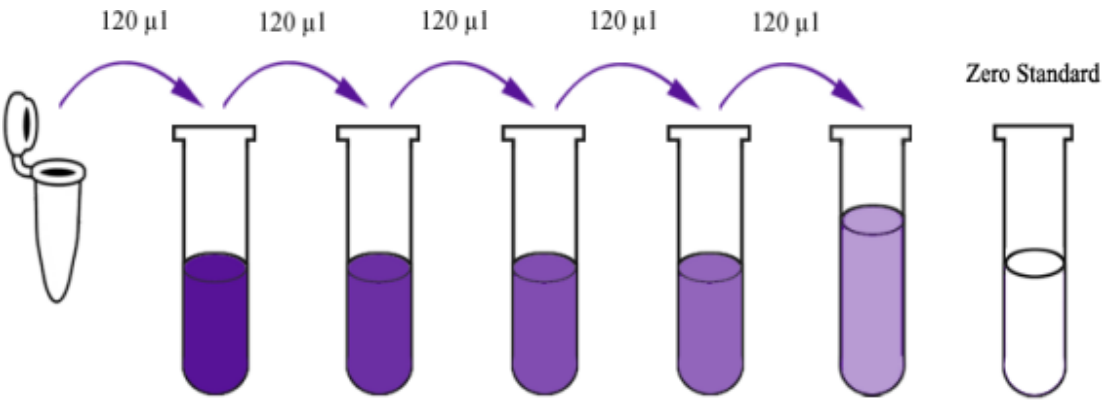
1- The plate had been per-coated with human IL-15 antibody.
2- The IL-15 present in the sample is added and binds to antibodies coated on the wells.
3- Is added Biotinylated human IL-15 antibody and binds to IL-15in the sample.
4- Is added The streptavidin-HRP and binds to the biotinylated IL-15 antibody.
5- After incubation unbound streptavidin-HRP is washing step.

6- Is added substrate solution and color develops in proportion to the amount of human IL-15.

7- The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Standard concentration: 1600ng/L

StandardNo.1	StandardNo.2	StandardNo.3	StandardNo.4	Standard No.5
50ng/L	100ng/L	200ng/L	400ng/L	800ng/L



3.4.3.2. Interleukin-12 (IL-12) Assay Procedure

Designed for accurate quantitative detection of interleukin-12 known IL-12 in the serum. The ELISA test is performed in the following steps:

1- The plate had been per-coated with human IL-12 antibody.

2- Is added The IL-12 present in the sample and binds to antibodies coated on the wells.

3- Is added Biotinylated human IL-12 antibody is added and binds to IL-12in the sample.

4- Is added The streptavidin-HRP is added and binds to the biotinylated IL-12 antibody.

5- After incubation, unbound streptavidin-HRP is washing step.
6- Is added Substrate solution and color develops in proportion to the amount of human IL-12.
7- The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Standard concentration: 80ng/L

StandardNo.1 StandardNo.2 StandardNo.3 StandardNo.4 Standard No.5 2.5ng/L 5ng/L 10ng/L 20ng/L 40ng/L

3.4.3.3. Interferon Gamma (IFN-ϒ) Assay Procedure

Designed for the accurate quantitative detection of interferon gamma known IFNG in the serum. The ELISA test is performed in the following steps:

1- The plate had been per-coated with human IFN-ϒ antibody.
2- Is added the IFN-ϒ present in the sample and binds to antibodies coated onthe wells.
3- Is added Biotinylated human IFN-ϒ antibody and binds to IFN-ϒ in the sample.
4- Is added the streptavidin-HRP and binds to the biotinylated IFNG antibody.
5- After incubation, unbound streptavidin-HRP is washing step.
6- Is added Substrate solution and color develops in proportion to the amount of human IFN-ϒ.
7- The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Standard concentration: 480ng/L

StandardNo.1 StandardNo.2 StandardNo.3 StandardNo.4 Standard No.5 15ng/L 30ng/L 60ng/L 120ng/L 240ng/L

3.5.Statistical analysis:

The statistical analysis was done by using SPSS program version 24 , The patients frequency , ANOVA and Chi-Square as well as ROC curve for sensitivity and specificity and Pearson correlation for certain parameters (Elliott and Woodward, 2007).

Chapter Four Results and Discussion

4.Distribution of studied parameters among vaccinated and Control Groups.

In the present study taking (85)vaccinated person with or without previous infection as a test group , in comparison with (35) person as old infection (Curied patients) mentioned as positive (+ve) control , with (30) healthy population as a negative (-ve) control groups , different parameters were studied to evaluation of immunological status after receiving complete doses of different vaccine , and revealed the following results .

4.1.The studied parameters level among test and studied groups:

Serology is an important pillar in the diagnostics of SARS-CoV-2 infection, especially when PCR may no longer be positive (Tre-Hardy *et al*.,2020).

There is a highly increased in IL-12, IL-15 and INF - γ levels in comparison with control groups (Cured and healthy) at Mean ±SD of IL-12 (26.24 ± 4.78, 6.0 ± 0.9 2, 6.04 ±0.95) The IL-15 level(596.84 ± 60.62 ,

294.53 ± 37.06 , 292.80 ± 39.11) , and INF – γ (143.29±50.92 , 54.92 ±

12.81 , 54.72 ± 11.92) respectively at (P value <0.001). As shown in Table (4 - 1). This result might be refer to that the increased in cytokine level expressed on cellular activity of immune system more effective against vaccine particles used instead of natural virus component.

cytokines that promote innate and adaptive immune response IFN- γ, IL-15, IL- 12, IL-23, tumor necrosis factor alpha TNF-α, IL-3, and IL-7 (Leonard *et al*., 2019).

Interleukin (IL)-12 is a pivotal cytokine that strongly stimulates Th1- associated cellular immunity. It is now recognized that IL-12 also activates humoral immunity to both T-dependent and T-independent antigens (Metzger,2010) IL-12 has also been shown to be very effective as a vaccine adjuvant for enhancement of protective antibody responses against pulmonary bacterial and viral infections, and is particularly effective when administered locally to mucosal surfaces, *i.e.*, intranasally (i.n.), together with vaccine(Baron *et al*.,2007) .

The IL-12 levels were observed to be significantly higher in the asymptomatic and mild disease groups than in the moderate and severe disease groups Similarly, (Xu *et al*., 2020). reported that serum IL-12 levels were comparable between patients with mild (classified as moderate in current study) and those with severe COVID-19 (Tjan *et al*.,2021).

The IL-15 immunotherapy may be a viable strategy for COVID-19, as it promotes innate immune responses via the induction of NK cells, $CD8^+$ T cells, and T regulatory cells to neutralize Th2 cytokine storms, resulting in decreased levels of IL-4, IL-5, and IL-13(Kandikattu *et al*.,2020).

The IL-15 is a critical immunoregulatory cytokine with anti-viral properties (Verbist *et al*.,2012). IL-15 is expressed by myeloid cells to aid in T cell responses, activate natural killer (NK) cells, and modulate inflammation (Kandikattu *et al*.,2019). Immune memory and reinfection remain non-elucidated.The pathogenesis of COVID-19 involves both humoral and cellular immunological responses, with cell-mediated immunity being discussed as the primary and most effective immune response to viral infection. It is supposed that COVID-19 vaccines also elicited effective cell immune response, and specifically IFNγ secreted by SARS-CoV-2-specific T-helper 1 and Tcytotoxic cells (Kurteva *et al*.,2022).

According to the literature, after suffering COVID-19, the development of immunity is observed for at least 1 year. Therefore, it would be logical to achieve similar results after vaccination (Hansen *et al*.,2021).

The study highlights the role of gamma interferon in the prevention of COVID-19 to study and identify its role and mechanism to prevent and treat COVID-19. Interferons contain antiviral factors that produce fibroblasts after viral infections in which interferon-inducible PKR kinase catalyzes RNA degradation. Innate cell-mediated immunity through NK cells that stimu-lates specific cytotoxic immunity based on the recognition of cell surface-bound viral antigens expressed in major histocompatibility complex (MHC) proteins that activate macrophages which therefore activates the anti-viral and antimicrobial activity of interferon-gamma. Therefore, COVID-19 being a newly emerging virus, with no approved effective drug or vaccine, an intimate understanding of the role of interferons in prevention is essential to implement novel therapeutic strategies.Previous studies suggest that serum levels of cytokines and chemokines are likely associated with the disease severity and clinical outcomes of COVID- 19 (Del Valle *et al*.,2020; Wang *et al*.,2021).

There was a low level of Anti SARS-COV-2 –IgM antibodies of both vaccinated and control groups ,while increased of Sars-cov2 –IgG in vaccinated population in comparison with curried patients and healthy control , at Mean ± SD (33.21 ± 16.06 , 20.36 ± 14.0 , 21.47 ± 13.77) in respective manner at

P. Value < 0.05.This result might be refer to that vaccination might induce specific IgG production rather than IgM .

During viral infection with SARS-CoV-2, the production of specific antibodies against the virus is consistent in most patients, except for

immune deficient patients. IgM can be detected as early as 3 days after infection and provides the first line of humoral immunity defense, after which high-affinity IgG responses are initiated and play a key role in long-term immune memory (Racine and Winslow, 2009).

The significance of antibody response in COVID-19 is important, not only in the diagnosis but also prognosis Specific antibodies, including IgG.

antibodies and neutralizing antibodies, are important for protecting the host from infection by blocking viral entry into host cells after viral infection (Nie *et al*.,2020).

The IgM antibody concentration reached a peak 10 days earlier than the IgG antibody concentration. The SARS-CoV-2 IgG antibodies maintained an upward trend after 20 days (Davies *et al*., 2020). Reported that IgM antibody levels peaked at10–12 days and significantly declined after 18 days (Padoan *et al*., 2020) which was similar to our study. IgG against COVID-19 has been reported to persist over seven weeks (Sethuraman *et al*., 2020) .

Some studies showed that COVID-19 patients with high IgG titres might produce neutralizing antibody activity, clearing the virus (Perera *et al*., 2020) reported a moderate correlation between Anti–SARS-CoV-2 spike protein IgG levels and neutralization titres in COVID-19 patient plasma (Xu *et al*., 2020).

In contrast, some studies observed higher levels of Anti-RBD IgG antibodies from COVID-19 patients that did not contribute to neutralization. Some studies suggest that Anti-RBD IgM and IgA also contribute to neutralization (Garcia-Beltran *et al*., 2021; Zhao *et al*., 2020).Since the virus-neutralizing antibody titre was determined by the virus infection inhibition rate, the content of neutralizing antibodies in the serum was found to be complex and is being recognized gradually (Barnes *et al.*, 2020).

Table (4 -1) The studied parameters level among test and studied groups.

Cytokines	Studied Groups		N	Mean ± (SD)	P.Vale
Interleukin - 12	Test	Vaccinated	85	26.24 ± (4.78)	.000
	Control	Cured	35	6.00 ±(0.92)	
		Healthy	30	6.04 ± (0.95)	
Interleukin - 15	Test	Vaccinated	85	596.84 ± (60.62)	.000
	Control	Cured	35	294.53 ± (37.06)	
		Healthy	30	292.80 ± (39.11)	
Interferon - γ	Test	Vaccinated	85	143.29 ± (50.92)	.000
	Control	Cured	35	54.92 ± (12.81)	
		Healthy	30	54.72 ± (11.92)	
Anti Sars -Cov2 IgM	Test	Vaccinated	85	0.06 ±0.10	.012
	Control	Cured	35	0.14 ±0.22	
		Healthy	30	0.13±0.22	
Anti Sars -Cov2 IgM	Test	Vaccinated	85	33.21 ±16.06	.000
	Control	Cured	35	20.36 ±14.00	
		Healthy	30	21.47 ±13.77	

4.2.The relationship between age groups and studied parameters level of Studied population:

The study explored the association between age and ability to neutralize virus by plotting the proportion of individuals whose sera produced detectable virus neutralization after the second dose at a given age.

Table (4 -2) show the age groups results of all studied groups adult age group > 60 years have lower level of cytokines (IL-12 , IL-15 and INF - γ in comparison with young and adult age groups in which they have higher level at P value . The result of patients at age > 60 years is relatively similar to result of control groups, this result might be show that the vaccinated population at these age groups have lower immunity

than other as well as low vaccine activity at this age, in regarding to cellular line activity of immune system. Vaccines designed to elicit protective immune responses remain the key hope for containing the COVID-19 pandemic caused by SARS-CoV-2. In particular, mRNA vaccines have shown excellent efficacy when administered as two doses separated by a three- or four-week gap (Polack *et al*., 2020; Baden *et al*.,2020).

There is increasing evidence that neutralizing responses are a correlate of protection (Khoury *et al*.,2021; Feng *et al*.,2021).

Few trial data on neutralizing responses or vaccine efficacy in individuals above the age of 80 are available1. This is even more pertinent for settings in which a dosing interval of 12–16 weeks or more has been implemented to maximize the administration of first doses. virus neutralization was lower in the older age group 22 days after the first dose. These data reflect the finding that responses to the ChAdOx1 nCov-19 (AZD- 1222) vaccine were lower in older than in younger mice, and the difference was overcome by booster dosing (Silva-Cayetano *et al*.,2020).

Individuals over 80 years of age differed from the younger group in four main respects that could explain poorer neutralization of SARS-CoV-2. First, serum IgG levels were lower, accompanied by a lower proportion of peripheral spike-specific IgG+ IgM− CD19+ memory B cells. Second, the elderly displayed lower somatic hypermutation in the BCR gene. Third, the elderly had lower enrichment for public BCR clonotypes that are associated with neutralization. Fourth, the older group displayed a marked reduction in IL-2-producing spike- reactive CD4+ T cells. Therefore, possible explanations for their poorer neutralizing responses include lower concentrations of antibodies (quantity) and/or lower-affinity antibodies (quality) resulting from B cell selection, reduced CD4+ T cell help, or a combination of both (Silva-Cayetano *et al*.,2020; Docherty *et al*.,2020).

The study showed that there were statistically significant differences between the age groups (20 - 29 years and > 60 years) have higher level of Anti – SARS-CoV-2- IgG while the IgM level was show that no difference in level after comparison with other age groups as well as control as the value of the P-value reached (0.108) . This result might be refer to that the vaccinated age > 60 years have more antibody production than other age groups and curried patients. As in the table (4 - 2). Age represents a key factor in COVID- 19 morbidity and mortality (Banerjee *et al*.,2020).

The generation of IgG antibodies against SARS-CoV-2 proteins might represent an applicable parameter for COVID-19 patient stratification. Nevertheless, the parallel between SARS-CoV2 sero-positivity and the clinical outcome is still a matter of investigation (Sun *et al*,.2020; Phipps *et al*.,2020).

Indeed, defined circulating factors - CXCL8, IL-10, IL-15, IL-27, and TNF-α - positively correlate with older age, longer hospitalization, and a more severe form of the disease and may thus represent the leading signature in critical (Angioni *et al*.,2020).

In study done by (Jalkanan *et al*.,2021) observed that practically all seronegative health care workers (20–65 years of age) responded to the first The BNT162b2 vaccine dose and an increase in spike protein-specific antibody responses in the IgG antibody class was detectable. The IgG antibody levels varied considerably and relatively few individuals showed increased antibody levels in the IgA and IgM antibody classes. The second vaccine dose, which was given according to the original vaccination protocol 3 weeks after the first vaccine dose, induced very high levels of spike protein-specific IgG antibodies, while IgA and IgM responses remained low.The vaccines' IgG antibody levels were on average higher than those seen in convalescent-phase sera of home-treated patients. Antibody responses have been found generally higher for COVID-19 patients with a more severe disease (Virtanen *et al*.,2021; Lynch *et al*.,2021; Grossberg *et al*.,2021).

Table (4-2) Age groups in relation to studied parameters level of studied groups.

Cytokines	Studied Groups	Age grouos	N	Mean ± SD	LSD
Interleukin – 12	Test (Vaccinated)	20 - 29 y	40	29.93 ± 4.99	7.99
		30 - 39	19	29.91 ± 6.57	
		40 - 49	9	18.74 ± 3.08	
		50 -59	12	21.94 ± 4.79	
		> 60 y	5	6.62 ± 3.34	
	Control (Healthy and Cured)	20 - 29 y	15	5.97 ± 0.75	
		30 -39	26	5.85 ± 0.96	
		40 -49	16	6.72 ± 0.78	
		50 -59	6	5.34 ± 0.42	
		> 60	2	4.97 ± 0.00	
Interleukin – 15	Test (Vaccinated)	20 - 29 y	40	570.30 ± 56.57	66.67
		30 - 39	19	729.69 ± 75.54	
		40 - 49	9	636.98 ± 33.98	
		50 -59	12	589.84 ± 26.80	
		> 60 y	5	248.80 ± 61.54	
	Control (Healthy and Curried)	20 - 29 y	15	282.62 ± 24.94	
		30 -39	26	299.18 ± 34.15	
		40 -49	16	307.67 ± 49.14	
		50 -59	6	273.03 ± 34.68	
		> 60	2	256.90 ± 0.00	
Interferon –γ	Test (Vaccinated)	20 - 29 y	40	143.07 ± 46.81	24.56
		30 - 39	19	185.67 ± 87.02	
		40 - 49	9	135.25 ± 46.51	
		50 -59	12	118.50 ± 32.12	
		> 60 y	5	57.91 ± 14.38	
	Control (Healthy and Cured)	20 - 29 y	15	54.18 ± 6.75	
		30 -39	26	51.70 ± 16.34	
		40 -49	16	56.20 ± 6.17	
		50 -59	6	63.40 ± 13.60	
		> 60	2	63.80 ± 0.00	
Anti Sars -Cov2 IgM	Test (Vaccinated)	20 - 29 y	40	0.05 ± 0.073	0.108
		30 - 39	19	0.07 ± 0.200	
		40 - 49	9	0.02 ± 0.027	
		50 -59	12	0.04 ± 0.036	
		> 60 y	5	0.09 ± 0.059	
	Control (Healthy and Cured)	20 - 29 y	15	0.02 ± 0.015	
		30 -39	26	0.16 ± 0.239	
		40 -49	16	0.20 ± 0.267	
		50 -59	6	0.19 ± 0.242	
		> 60	2	0.04 ± 0.000	
Anti Sars -Cov2 IgG	Test (Vaccinated)	20 - 29 y	40	37.56 ± 15.012	8.77
		30 - 39	19	28.73 ± 18.70	
		40 - 49	9	28.78 ± 14.06	
		50 -59	12	29.53 ± 16.61	
		> 60 y	5	37.27 ± 11.19	
	Control (Healthy and Cured)	20 - 29 y	15	14.99 ± 13.75	
		30 -39	26	22.41 ± 12.26	
		40 -49	16	22.63 ± 16.95	
		50 -59	6	18.81 ± 7.62	
		> 60	2	27.14 ± 0.00	

4.3. The relationship between gender studied parameters level of Studied groups:

The male population have higher level of the cytokines (IL-12, IL-15 and INF – γ) level in comparison with female in both vaccinated and control groups (curried and healthy population). This result listed in table (4 - 3). This result might be refer to that , the male patients might be have immune activity more than female in relation to cellular type of immune response . This result in table (4-3) mentioned The difference between vaccinated female have higher level of Anti-Sars-Cov 2 IgG antibody rather than male , the specific IgM have no differences at both male and female as well as control samples. This result might be refer to that female patients induce antibody production more than male. The higher incidence and higher mortality rate of COVID-19 in men compared to women is due to differences in biological factors (including differences in DNA, reproductive organs, and steroid hormones), and gendered-related issues such as practicing the traditional and social aspects (Gebhard *et al*., 2020).

Previous researches demonstrated that sex could have a significant impact on infection outcomes and was linked to fundamental variations in immune responses to the diseases in human (Fischer *et al*., 2015; Klein and Flanagan, 2016; Safdar *et al*., 2021).

Table (4 - 3) The relationship of gender and studied parameters in studied population.

Cytokines	Studied Groups	Gender	N	Mean± SD	P. Value
Interleukin – 12	Test (Vaccinated)	Male	45	33.73± 5.67	.000
		Female	40	17.83± 2 .02	
	Control	Male	50	6.06± 1.00	
		Female	15	5.87± 0.59	
Interleukin – 15	Test (Vaccinated)	Male	45	701.57± 51.48	.000
		Female	40	479.01± 43.78	
	Control	Male	50	290.59± 37.94	
		Female	15	304.22± 36.29	
Interferon –γ	Test (Vaccinated)	Male	45	175.45 ± 59.51	.000
		Female	40	107.10± 33.47	
	Control (+ve and –ve)	Male	50	54.58± 13.40	
		Female	15	55.66± 7.94	
Anti Sars -Cov2 IgM	Test (Vaccinated)	Male	45	0.05 ± 0.06	.000
		Female	40	0.06 ± 0.14	
	Control	Male	50	0.17 ± 0.24	
		Female	15	0.02 ± 0.01	
Anti Sars -Cov2 IgG	Test (Vaccinated)	Male	45	32.15 ± 16.36	.000
		Female	40	34.41 ± 15.84	
	Control	Male	50	22.22 ± 13.71	
		Female	15	16.36 ± 13.57	

4.4. The effect of Smoking on studied parameters level of Studied population:

The smoking population have a second factor in which that enhancement of cellular activity of immune response as like as viral infection , the level of cytokines (IL-12 , IL-15 and INF - γ) show that elevated level in smoking groups in comparison with non smoking as well as with curried and healthy control groups, as shown in table (4-4). NK cells are highly responsive to IL-12 which triggers IFN-γ production via STAT4 phosphorylation and Tbet transcriptional activity (Koch *et al*.2007; Morinobu *et al*.,2002).The role of IL-12 in NK-cell biology has been extensively reviewed elsewhere (Fehniger and

Cooper,2016). The result of table (4-4) were show that the smoking population have induced antibody production more than nonsmoking one , while there is no Specific IgM antibody differences at all smoking and nonsmoking of both studied and control groups.

The health consequences of smoking include a wide range of illnesses, being a risk factor for lung cancer, chronic obstructive pulmonary disease, cardiovascular diseases, viral and bacterial infections of the respiratory system, and others (US Department of Health and Human Services, 2014).

The vast majority of the current body of evidence suggests that smoking has a negative impact on the humoral response to COVID-19 vaccines, with both potential lower response and more rapid lowering of the vaccine-elicited IgG titers. However, the literature available so far does not allow us to firmly ascertain whether the effect is related to duration of smoking or number of cigarettes smoked per day (Yamamoto *et al*.,2021; Ferrara *et al*.,2022).

The negative effects played by smoking on the immune system seem to be determined by several mechanisms that influence both innate and adaptive immunity. Regarding the first, certain studies have indicated a direct effect of smoking on alterations in immune cell counts (including monocytes, macrophages, dendritic cells, and lymphocytes), but the effect of the complex mixture of tobacco chemicals varies depending on the individual smoking habits, as well as several subsets of cells explored in different studies (Edwards,2009).

In cigarettes smokers, the T cells also exhibit differences in proliferation response, indicating defective adaptive immunity responses. Furthermore, analyses of Ig revealed a decreased production of IgA, IgG, and IgM associated with smoking (Pedersen *et al*.2019; Ferrara *et al*.,2022).

It is worth also mentioning that some studies included in this review did not detect a correlation between smoking status and postvaccination IgG titres. However, most of these reports include a very low sample size and/or proportion of smokers, or examined the antibody levels in the early weeks after the completion of vaccination cycle (Gümü¸s *et al*.,2021; Modenese, *et al*.,2021; Pedersen *et al*.,2019). making it difficult to appreciate possible differences between smokers and nonsmokers (Ferrara *et al*.,2022).

Table (4 -4) The effect of Smoking on studied parameters level of Studied population

Cytokines	Studied Groups	Smoker	N	Mean± SD	P, Value
Interleukin – 12	Test (Vaccinated)	Smoking	23	28.64± 6.42	.000
		NonSmoking	62	25.35 ± 4.30	
	Control	Smoking	35	5.86 ± 0.89	
		NonSmoking	30	6.21 ± 0.94	
Interleukin – 15	Test (Vaccinated)	Smoking	23	724.57 ± 72.57	.000
		NonSmoking	62	549.45 ± 51 .10	
	Control	Smoking	35	289.74 ± 30.01	
		NonSmoking	30	298.39 ± 45.21	
Interferon –γ	Test (Vaccinated)	Smoking	23	156.53 ± 59.18	.000
		NonSmoking	62	138.37 ± 48.78	
	Control	Smoking	35	52.02 ± 14.32	
		NonSmoking	30	58.10 ± 8.57	
Anti Sars -Cov2 IgM	Test (Vaccinated)	Smoking	23	0.05 ± 0.05	.000
		NonSmoking	62	0.06 ± 0.12	
	Control	Smoking	35	0.21 ± 0.25	
		NonSmoking	30	0.05 ± 0.14	
Anti Sars -Cov2 IgG	Test (Vaccinated)	Smoking	23	38.42 ± 12.42	.000
		NonSmoking	62	31.28 ± 16.90	
	Control	Smoking	35	26.07 ± 11.46	
		NonSmoking	30	14.81 ± 9.99	

4.5.Study the Effect of vaccine duration on the Immunological Parameters:

Follow-up time after full vaccination of only 2–3 months or more . Estimates of vaccine effectiveness among people vaccin-ated as part of national vaccine rollouts were similar to the efficacy results in the first few months after vaccine introduction. Assessing the duration of protection for COVID-19 vaccines over longer time periods, however, requires continued monitoring. Knowing whether and to what extent vaccine effectiveness wanes is crucial to inform vaccine policy decisions, such as the need for, timing, and target populations for booster doses.

The results in Table (4-5) showed that there were statistically significant differences between the time of doses. The study showed that there are statistically significant differences in the effectiveness of the vaccine between the periods after taking the vaccine for the two studied vaccines

It was showed that the decline in vaccine efficacy or effectiveness against severe COVID-19 disease with timelines vaccination was less than that for SARS-CoV-2 infection and symptomatic COVID-19 disease and the average change in vaccine efficacy or effectiveness over time was estimated using a linear mixed-effects model for the repeated measures within each studyvaccine group

A decrease in the vaccine efficacy or effectiveness over time has three potential explanations the decrease reflect lower vaccine efficacy or effectiveness against a new variant true waning immunity caused by loss of vaccine-induced immunological protection or bias(Feikin *et al*.,2 022).

Some study finding is consistent with immunological data showing that over time, amounts of most vaccine-derived antibodies, including those that neutralise the virus, decline (Dolgin,2021; Hamady *et al*.,2021).

Because the immune system forms memory cells that can be activated upon exposure to a virus and includes cellular immunity, it is not clear, whether this observed antibody decay results in diminished vaccine efficacy or effectiveness, and if so, over what timeframe and against which outcomes. Immunity comes from evidence showing that after giving a booster dose the vaccine efficacy or effectiveness increases compared with people who had only received the primary vaccine series (Bar-On *et al*.,2021; Barda *et al*.,2021).

It has been shown that with increasing time since full vaccination, the viral load of breakthrough infections increases, but becomes lower again soon after booster vaccination(Levine-Tiefenbrun *et al*.,2021).

The two-dose COVID-19 vaccination campaign substantially reduced hospitalisations and deaths despite high infection rates (Cabezas *et al*.,2021; Haas *et al*.,2022). However, the effectiveness against infection, as happens also for other vaccines, wanes within months of the second dose (Levin *et al*.,2021; Shekhar *et al*.,2021).

Studies in Qatar showed substantial waning, in effectiveness against SARS-CoV-2 infection from month 4 after the second dose for BNT162b2 (tozinameran; Pfizer-BioNtech) (Tang *et al*.,2021; Chemaitelly *et al*.,2021).

A systematic review of 39 studies showed vaccine effectiveness against symptomatic SARS-CoV-2 infection in the general population to be 89–97% for BNT162b2, 92% for ChAdOx1 nCoV-19 (Oxford-AstraZeneca), and 94% for mRNA-1273(Cheng *et al*.,2021).

Vaccine effectiveness has been reported to drop to 44·1% with ChAdOx1 nCoV-19 or to 62·5% with BNT162b2 by week 20 after the second dose(10,11). Risk of infection also increased considerably 6 months after vaccination in data from the National Israeli database

(Goldberg *et al*.,2021).

A booster dose of the BNT162b2 vaccine reduced the rates of both infection and severe COVID-19 illness in the Israeli population older than 60 years16 and overall (Barda.,2021). Boosters of mRNA-based vaccines were also safe and effective in randomised controlled trials,(Munro *et al*.,2021; Liu *et al*.,2021) with good immunogenicity observed for both homologous and heterologous booster doses. After receiving a booster dose, protection against symptomatic infection increased to over 93·1%,10,11 resulting in a proposed regimen of universal boosters 6 months after the second dose (LaFraniere *et al*.,2021; Menni *et al*., 2022).

Table (4 – 5) Study the Effect of vaccine duration on the Immunological Parameters.

Vaccine type		**IgM antibody**	**IgG Antibody**
		Mean	**Mean**
Cinopharm Vac	2 Weak - 1 Month	.06	11.85
	2 month - 3 M	.02	20.70
	4 Mpnth - 5 Month	.05	27.93
	> 5 Month	.03	32.68
***p-value**		0.277 N.S	0.156 N.S
Faizer Vac	2 Weak - 1 Month	.10	42.05
	2 month - 3 M	.08	40.89
	4 Mpnth - 5 Month	.06	43.23
	> 5 Month	.06	49.51
*p-value		0.972 N.S	0.872 N.S

4.6.The Covid -19 infection and studied parameters level of Studied population :

The cytokines (IL-12 , IL-15 and INF - γ) level among infected population after receiving vaccine have higher level than non infected person and repeated more than one infection , as like as the control groups curried and healthy population, at P Value < 0.05 . The table (4-6) show these results . This result might be refer to that the SARS-COV-2 virus might be induce reactive immunity after exposure to first infection after receiving the vaccination doses , at cellular types by increased level of certain cytokines such as IL-12 , IL-15 and INF – γ. Recurrent infection does not provide the optimum immunity against such infection in regarding to the present study .

The result of table (4-6) show that the Non infected Vaccinated population have high level of Anti SARS-COV-2 IgG antibody in comparison with infected population , This result might be refer to that the using of vaccine revealed IgG level more than infected vaccinated population , this might be due to the random viral dose doesn't give complete protection against virus , while the constant vaccine doses do that by increased the memory B-Cells and enhancement of specific IgG production

Table (4 – 6) The Covid -19 infection and studied parameters level of Studied population .

Cytokines	Studied Groups	Covid – infection	N	Mean ± SD	LSD
Interleukin -12	Test (Vaccinated)	Infected	41	26.66 ± 5.99	.000
		Non Infected	44	25.86 ± 3.90	
	Control	Cured	35	6.04 ± 0.84	
		Healthy	30	6.01 ± 0.95	
Interleukin -15	Test (Vaccinated)	Infected	41	639.76 ± 93.78	.000
		Non Infected	44	556.84 ± 53 .61	
	Control	Cured	35	296.04 ± 22.20	
		Healthy	30	293.10 ± 41.13	
Interferon – γ	Test (Vaccinated)	Infected	41	149.88 ± 53.51	.000
		Non Infected	44	137.14 ± 49.97	
	Control	Cured	35	62.96 ± 14.21	
		Healthy	30	52.60 ± 10.86	
Anti Sars -Cov2 IgM	Test (Vaccinated)	Infected	41	0.04 ± 0.05	.000
		Non Infected	44	0.07 ± 0.14	
	Control	Cured	35	0.56 ± 0.05	
		Healthy	30	0.02 ± 0.01	
Anti Sars -Cov2 IgG	Test (Vaccinated)	Infected	41	31.65 ± 17.32	.000
		Non Infected	44	34.66 ± 14.85	
	Control	Cured	35	30.53 ± 4.47	
		Healthy	30	18.22 ± 14.33	

4.7 Relationship of recurrent infection and studied parameters level of Studied population:

The cytokines (IL-12 , IL-15 and INF - γ) level among infected population after receiving vaccine have higher level than non-infected person and repeated more than one infection , as like as the control groups curried and healthy population, at P Value < 0.05 . The Table (4-7) show these results. This result might be refer to that the Sars-Cov2 virus might be induce reactive immunity after exposure to first infection after receiving the vaccination doses , at cellular types by increased level of certain cytokines such as IL-12 , IL-15 and INF – γ. Recurrent infection does not provide the optimum immunity against such infection in regarding to the present study .

The result of table (4-7) show that the Non infected Vaccinated population have high level of Anti SARS-COV-2 IgM antibody in comparison with infected population , This result might be refer to that the using of vaccine

revealed IgG level more than infected vaccinated population .

Table (4 – 7) Relationship of recurrent infection and studied parameters level of Studied population .

Cytokines	Studied Groups	Recurrent infection	N	Mean± SD	LSD
Interleukin -12	Test (Vaccinated)	No infection	44	25.86 ± 3.90	.000
		One time	35	28.62 ± 7.64	
		Two time	6	15.24 ± 4.97	
	Control	Healthy	30	6.31 ± 0.89	
		One infection (Cured)	35	5.80 ± 0.90	
Interleukin -15	Test (Vaccinated)	No infection	44	556.84± 53 .61	.000
		One time	35	718.42± 60 .04	
		Two time	6	180.88± 48.19	
	Control	Healthy	30	302.61± 43.80	
		One infection (Cured)	35	287.01± 31.37	
Interferon – γ	Test (Vaccinated)	No infection	44	137.14 ± 49.97	.000
		One time	35	166.76 ± 60.34	
		Two time	6	51.41 ± 8.74	
	Control	Healthy	30	58.94 ± 8.25	
		One infection (Cured)	35	51.72 ± 13.98	
Anti Sars -Cov2 IgM	Test (Vaccinated)	No infection	44	.0748± .14151	.000
		One time	35	.0480± .05572	
		Two time	6	.0233± .02066	
	Control Cured and Healthy	Healthy	30	.0611± .14987	
		One infection (Cured)	35	.2049± .24820	
Anti Sars -Cov2 IgG	Test (Vaccinated)	No infection	44	34.66 ± 14.85	.000
		One time	35	30.95 ± 17.00	
		Two time	6	35.74 ± 20.32	
	Control Cured and Healthy	Healthy	30	14.68 ± 14.49	
		One infection (Cured)	35	.56± 11.34	

4.8.Rapid detection of anti-Sars - IgM Antibody and studied parameters level of Studied population:

The result of cytokines (IL-12,IL-15and INF-γ)level among population having negative rapid test for anti Sars –IgM antibody revealed high cytokines rather than positive IgM antibody , this result might be refer to that the vaccine doses induce cytokine production more than infected with Sars- Cov2 virus.This result were listed in Table (4-8).

The result of table (4-8) show that the positive IgM antibody in Vaccinated population have high level of Anti -SARS-COV-2 IgG antibody in comparison with infected population , This result might be refer to that the using of vaccine revealed IgG level more than infected vaccinated population .

Table (4 - 8) Rapid detection of anti-Sars - IgM Antibody and studied parameters level of Studied population.

Cytokines	Studied Groups	Rapid IgM	N	Mean± SD	LSD
Interleukin -12	Test (Vaccinated)	Anti-IgM +ve	15	23.34 ± 5.17	.000
		Anti-IgM –ve	70	26.87 ± 4.83	
	Control	Anti-IgM +ve	14	6.04 ± 0.84	
		Anti-IgM –ve	51	6.01 ± 0.95	
Interleukin -15	Test (Vaccinated)	Anti-IgM +ve	15	533.99± 52.82	.000
		Anti-IgM –ve	70	610.30± 57.32	
	Control	Anti-IgM +ve	14	296.04± 22.20	
		Anti-IgM –ve	51	293.10± 41.13	
Interferon – γ	Test (Vaccinated)	Anti-IgM +ve	15	136.71± 42.37	.000
		Anti-IgM –ve	70	144.69± 53.63	
	Control	Anti-IgM +ve	14	62.96± 14.21	
		Anti-IgM –ve	51	52.60± 10.86	
Anti Sars -Cov2 IgM	Test (Vaccinated)	Anti-IgM +ve	15	0.14± 0.08	.000
		Anti-IgM –ve	70	0.04± 0.10	
	Control	Anti-IgM +ve	14	0.56± 0.05	
		Anti-IgM –ve	51	0.02± 0.01	
Anti Sars -Cov2 IgG	Test (Vaccinated)	Anti-IgM +ve	15	36.69± 12.03	.000
		Anti-IgM –ve	70	32.47± 16.78	
	Control	Anti-IgM +ve	14	30.53± 4.47	
		Anti-IgM –ve	51	18.22± 14.33	

4.9 . The relationship between Rapid anti –Sars-cov2 - IgG and studied parameters level of Studied population:

The result of anti –Sars –Cov 2 IgG antibody revealed different score of result , low , moderate , and strong or high score reaction , the cytokine (IL-12) level were show elevated in population at low IgG antibody detection by rapid method , while both cytokines (IL-15 and INF - γ) the level were increased at population in which have high IgG antibody . as mentioned in Table (4 – 9)

There is association with qualitative antibody at high IgG score with the quantitative level of the anti-Sars –Cov 2 –IgG antibody and revealed high titer level that other qualitative score of low and moderate IgG antibody as well as control population . as in Table (4 - 9) .

Table (4 - 9) The relationship between Rapid anti –Sars-cov2 - IgG and studied parameters level of Studied population

Cytokines	Studied Groups	Rapid IgG Score	N	Mean ± SD	LSD
Interleukin – 12	Test (Vaccinated)	Low IgG	16	29.43 ± 5.42	1.49
		Mod IgG	11	27.93 ± 3.06	
		High IgG	49	27.93 ± 6.37	
		No Titer	9	9.32 ± 5.87	
	Control (Healthy And Cured)	Low IgG	12	5.88 ± 1.07	
		Mod IgG	8	5.36 ± 0.29	
		High IgG	15	6.06 ± 0.87	
		No titer IgG	30	6.45 ± 0.92	
Interleukin – 15	Test (Vaccinated)	Low IgG	16	540.83 ± 54.21	91.55
		Mod IgG	11	449.27 ± 34.38	
		High IgG	49	704.96 ± 2.55	
		No Titer	9	288.09 ± 84.05	
	Control (Healthy And Cured)	Low IgG	12	279.11 ± 29.69	
		Mod IgG	8	301.00 ± 31.89	
		High IgG	15	278.70 ± 31.36	
		No titer IgG	30	326.85 ± 36.65	
Interferon – γ	Test (Vaccinated)	Low IgG	16	134.63 ± 140.91	2.92
		Mod IgG	11	131.70 ± 147.71	
		High IgG	49	165.05 ± 164.08	
		No Titer	9	54.32 ± 31.10	
	Control (Healthy And Cured)	Low IgG	12	42.92 ± 13.10	
		Mod IgG	8	72.85± 7.59	
		High IgG	15	51.70 ± 5.04	
		No titer IgG	30	60.75 ± 4.98	
Anti Sars -Cov2 IgM	Test (Vaccinated)	Low IgG	16	0.03 ± 0.03	0.01
		Mod IgG	11	0.10 ± 0.26	
		High IgG	49	0.06 ± 0.06	
		No Titer	9	0.01 ± 0.01	
	Control (Healthy And Cured)	Low IgG	12	0.02 ± 0.01	
		Mod IgG	8	0.40 ± 0.22	
		High IgG	15	0.19 ± 0.25	
		No titer IgG	30	0.021 ± 0.01	
Anti Sars -Cov2 IgG	Test (Vaccinated)	Low IgG	16	17.50 ± 7.85	6.65
		Mod IgG	11	32.52 ± 11.69	
		High IgG	49	43.24 ± 6.51	
		No Titer	9	7.40 ± 17.61	
	Control (Healthy And Cured)	Low IgG	12	11.83 ± 3.65	
		Mod IgG	8	25.87 ± 1.62	
		High IgG	15	35.33 ± 5.10	
		No titer IgG	30	3.95 ± 2.57	

4.10. The relationship between types of vaccine and studied parameters level of Studied population:

The cytokines level of vaccinated population with Pfizer vaccine in tow related doses show higher levels than cinopharm vaccine , the highest level were recorded of (IL-12 , IL-15 and INF - γ) in Pfizer vaccinated population as well as control . as shown in table (4 - 10) . This relation were introduce to reach the anti Sars–IgG antibody level in which that revealed high level than cinopharm vaccine as in table(4 -10). This result might be show that the Pfizer vaccine induce more protection that cinopharm at the cellular and humeral immune reactivity .

Table (4 - 10) The relationship between types of vaccine and studied parameters level of Studied population .

Cytokines	Studied Groups	Vaccine Types	N	Mean± SD	LSD
Interleukin -12	Test (Vaccinated)	Pfizer	45	36.15 ± 4.52	.000
		Cinopharm	40	15.10 ± 2.09	
	Control	Control(Non Vac)	65	6.0240 ± 0.92	
Interleukin -15	Test (Vaccinated)	Pfizer	45	693.33 ± 59.90	.000
		Cinopharm	40	488.28 ± 43.52	
	Control	Control(Non Vac)	65	293.73 ± 37.73	
Interferon –γ	Test (Vaccinated)	Pfizer	45	181.11 ± 171.91	.000
		Cinopharm	40	100.74± 110.48	
	Control	Control(Non Vac)	65	54.83 ± 12.31	
Anti Sars -Cov2 IgM	Test (Vaccinated)	Pfizer Vac	45	0.08 ± 0.14	.006
		Cinopharm Vac	40	0.03 ± 0.03	
	Control	Control(Non Vac)	65	0.14 ± 0.22	
Anti Sars -Cov2 IgG	Test (Vaccinated)	Pfizer Vac	45	41.70 ± 11.58	.000
		Cinopharm Vac	40	23.66 ± 15.10	
	Control	Control(Non Vac)	65	20.87 ± 13.80	

4.11.Correlation between all studied parameters:

4.11.1.Correlation of IL- 12 and INF – γ among Studied groups (Vaccinated) :

There is a direct correlation between IL-12 and INF – γ among studied groups , this result might be refer to that increased in IL-12 lead to enhancement or increased in INF – γ , both of them are cellular cytokines make a role in regulation of cellular activity of the immune system . The Figure (4-1) show this result.

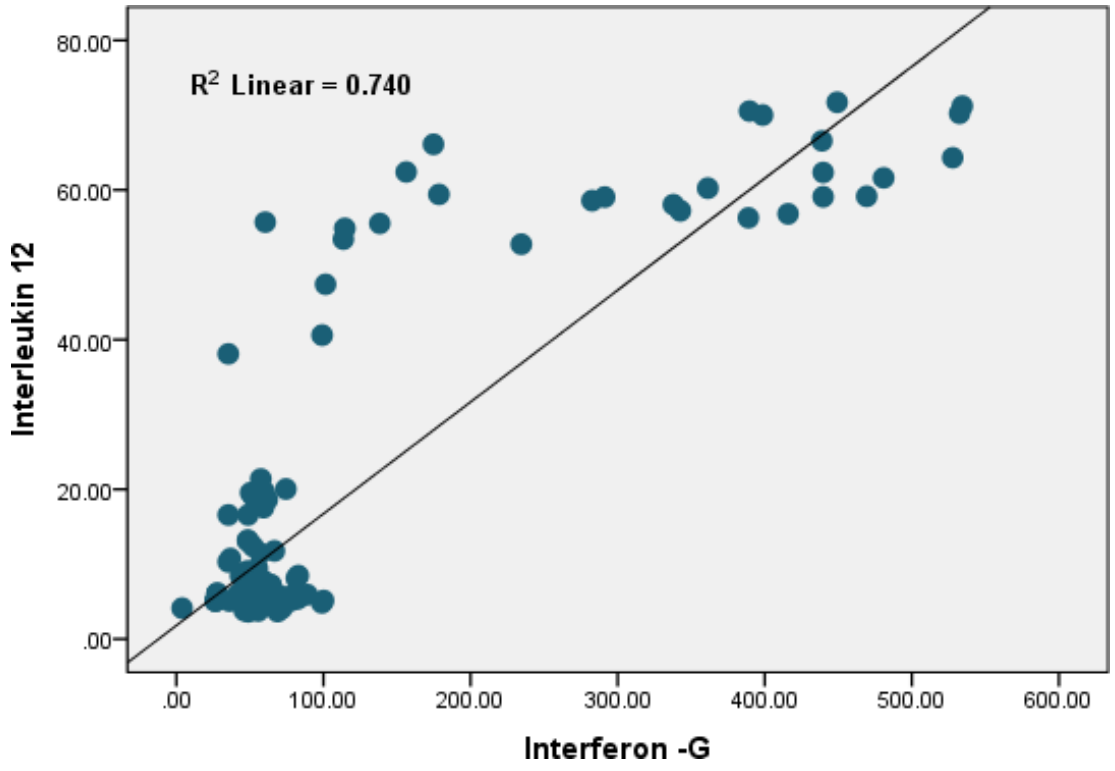


Figure (4-1)Correlation of IL- 12 and INF – γ among Studied Groups

4.11.2.Correlation of IL- 12 and IL- 15 among Studied groups (Vaccinated) :

There is a direct correlation between IL-12 and IL-15 among studied groups , this result might be refer to that increased in IL-12 lead to enhancement or increased in IL-15 , both of them are cellular cytokines make a role in regulation of cellular activity of the immune system .The Figure (4-2) show this result.

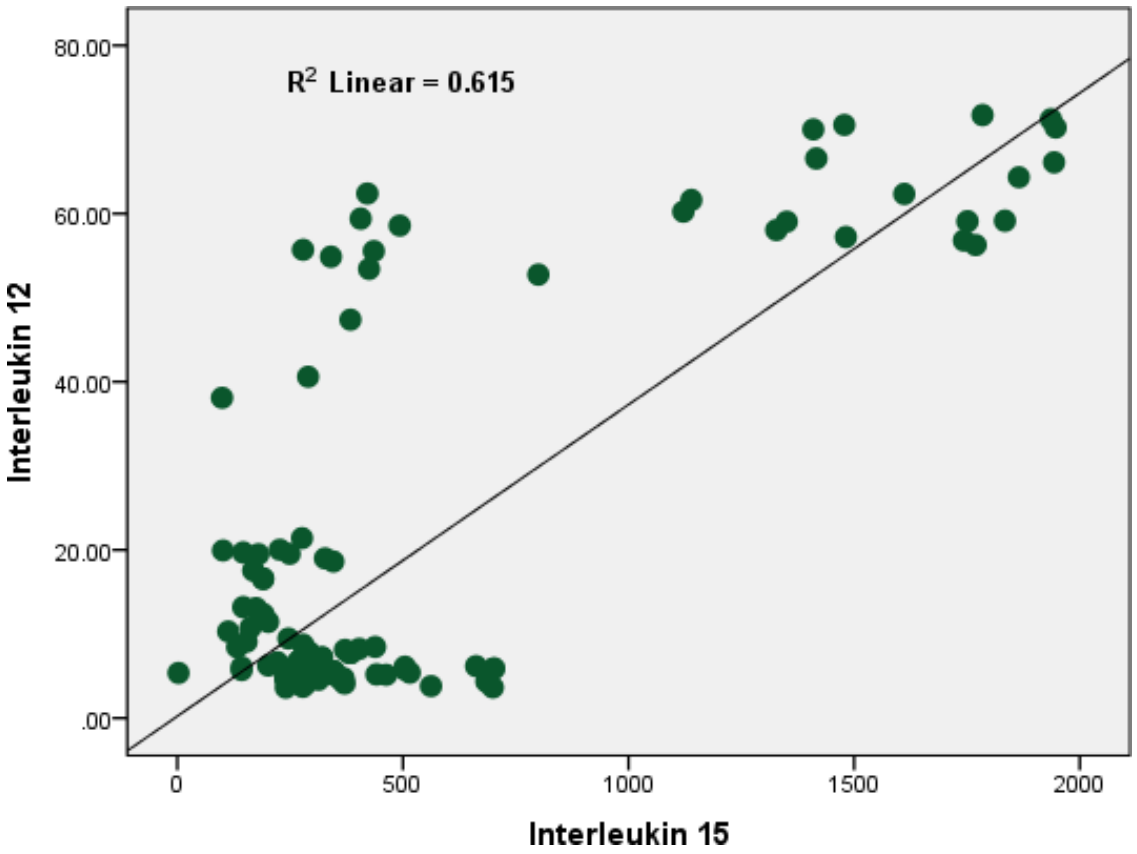


Figure (4-2) Correlation of IL- 12 and IL- 15 among Studied Groups.

4.11.3.Correlation of IL- 12 and anti SARS-COV-2 IgM antibody among Studied Groups (Vaccinated) :

The Figure (4-3)show that indirect or negative correlation between IL- 12 and Anti –IgM antibody level , this result might be show that increased IL- 12 production earlear than antibody production or in the first few days of infection while antibody need mre time to produce .

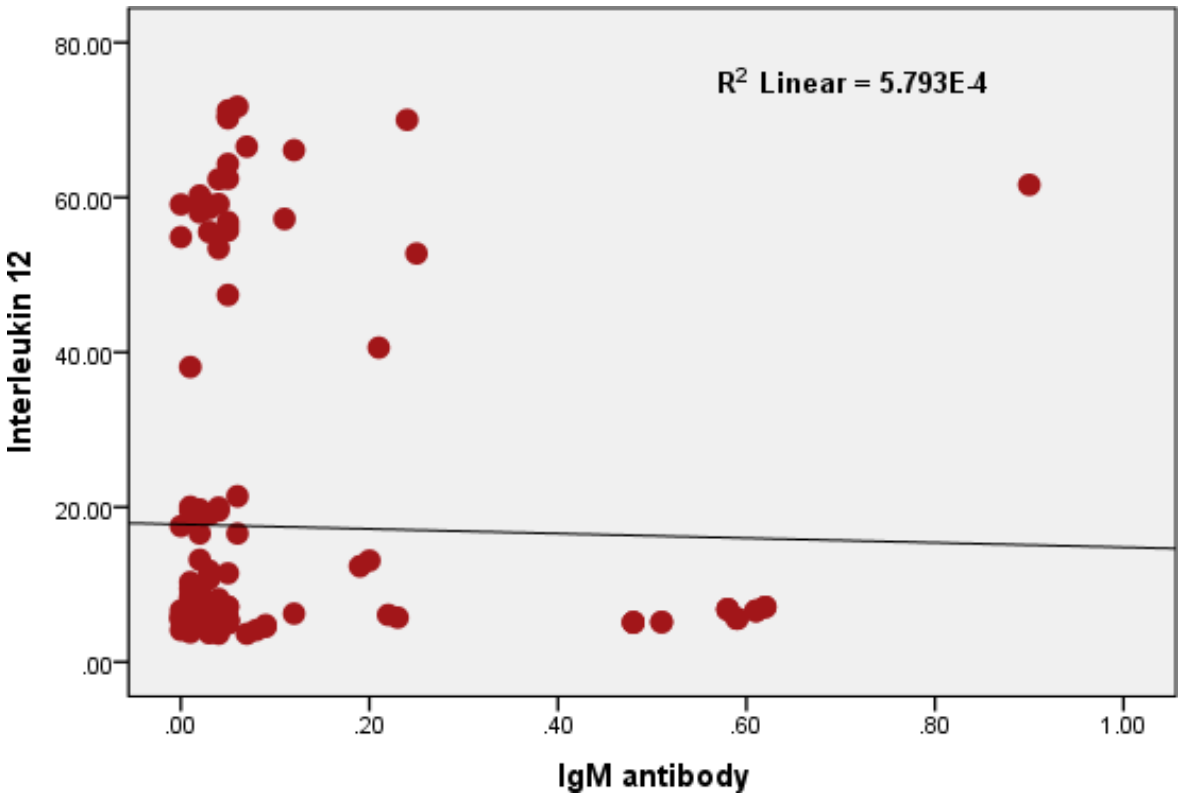


Figure (4-3) Correlation of IL- 12 and anti SARS-COV-2 IgM Antibody among Studied Groups

4.11.4.Correlation of IL- 12 and anti- SARS-COV-2 IgG Antibody among Studied Groups (Vaccinated) :

The figure (4-4) show that direct or positive correlation between IL-12 and Anti –IgG antibody level , this result might be show that increased IL-12 production enhancement of antibody production , especially in late infection because the IgG was produced later than cytokines and other antibodies such IgM .

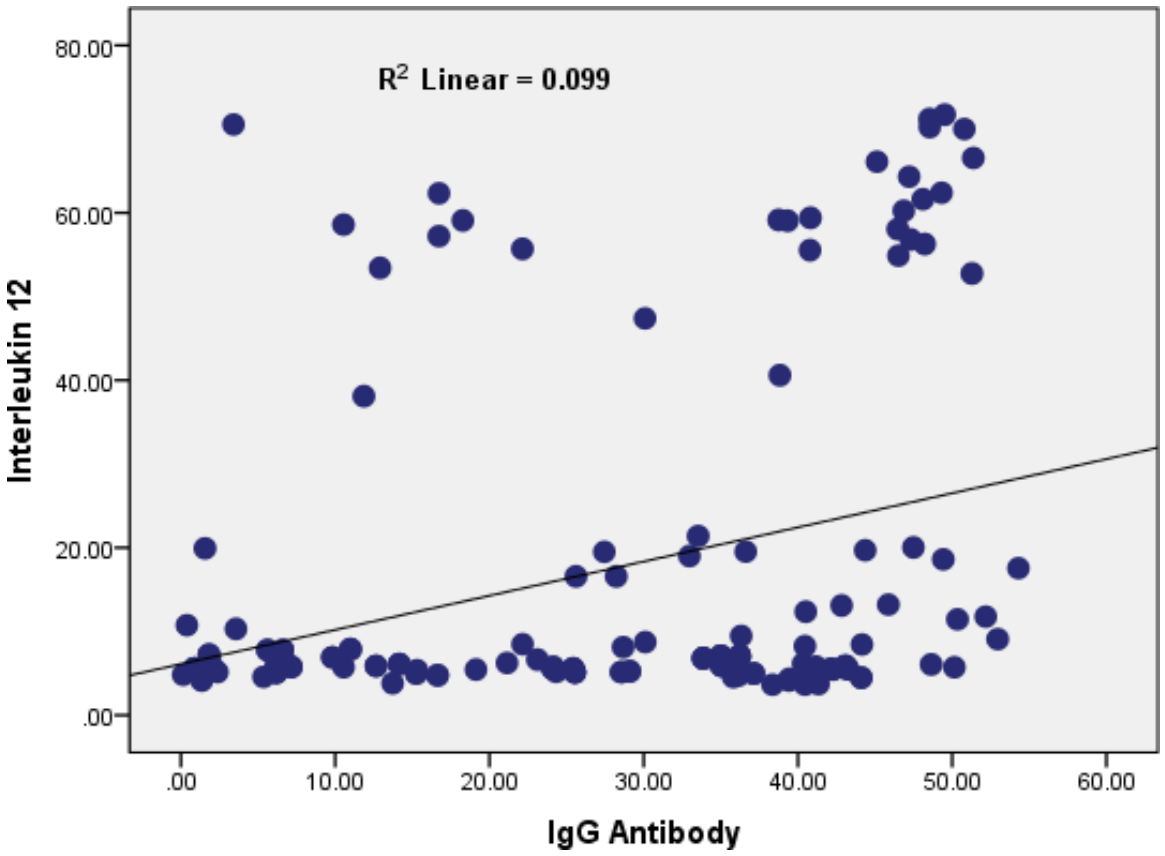


Figure (4-4) Correlation of IL- 12 and Anti -SARS-COV-2 IgG antibody among Studied Groups

4.11.5.Correlation of IL- 15 and INF – γ among Studied groups (Vaccinated) :

There is a direct correlation between IL-15 and INF – γ among studied groups this result might be refer to that increased in IL-15 lead to enhancement or increased in INF – γ both of them are cellular cytokines make a role in regulation of cellular activity of the immune system . The figure (4-5)show this result.

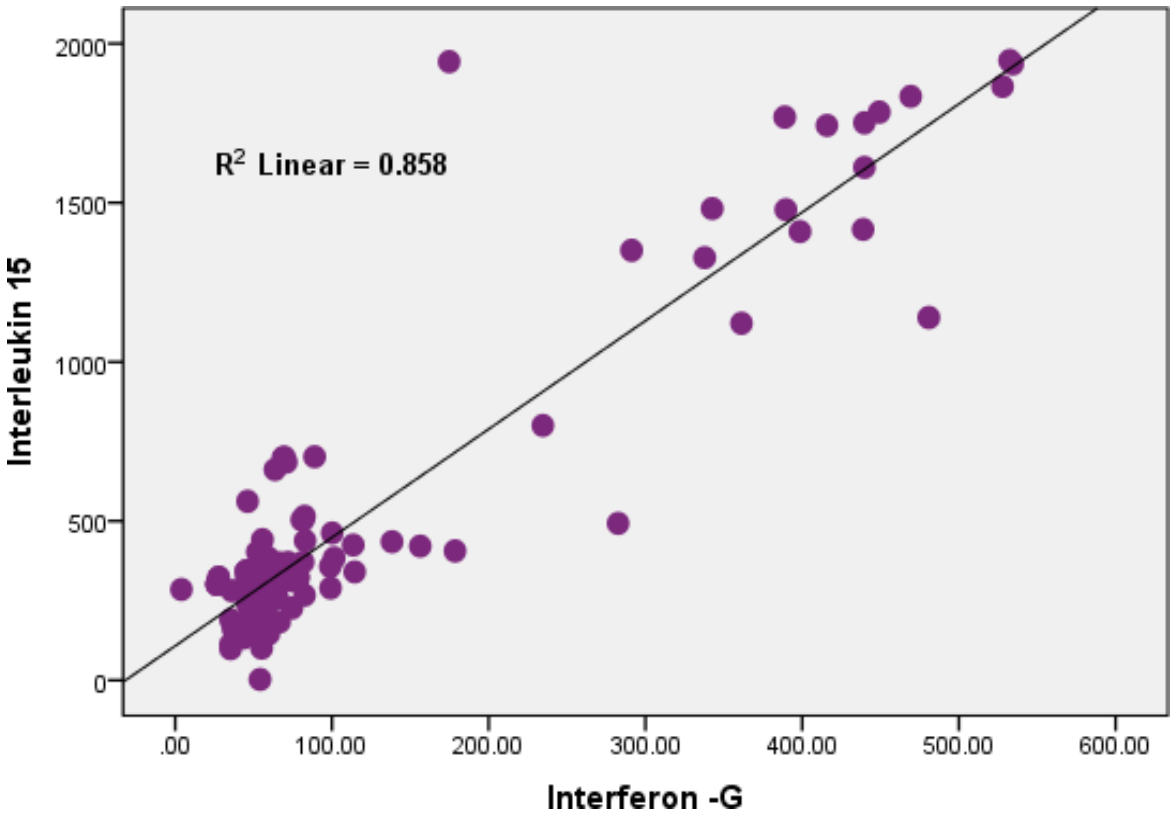


Figure (4-5) Correlation of IL- 15 and INF – γ among Studied Groups .

4.11.6.Correlation of IL- 15 and anti- SARS-COV-2 IgM antibody among Studied Groups (Vaccinated) :

As like as IL-12 , the figure (4-6) show that indirect or negative correlation between IL-15 and Anti –IgM antibody level , this result might be show that increased IL-15 production earlear than antibody production or in the first few days of infection .

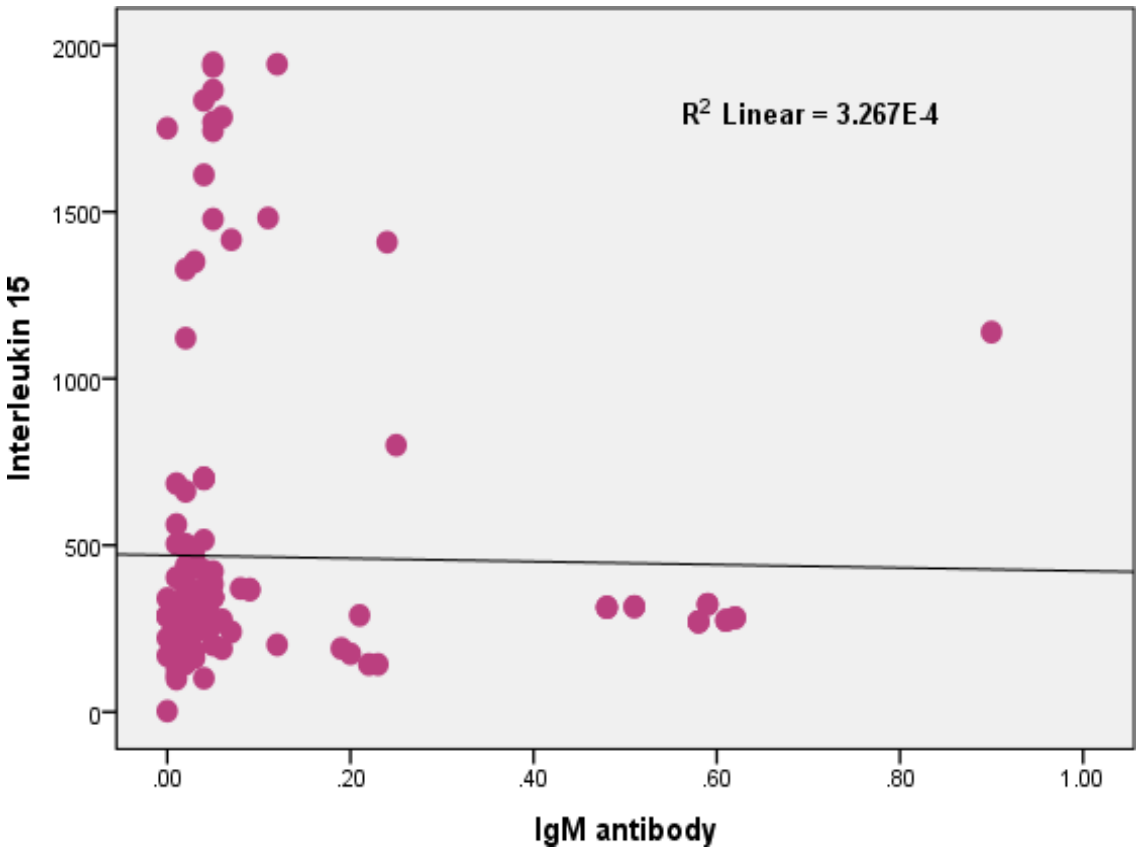


Figure (4-6) Correlation of IL- 15 and anti- SARS-COV-2 IgM antibody among Studied Groups .

4.11.7.Correlation of IL- 15 and anti- SARS-COV-2 IgG Antibody among Studied Groups (Vaccinated) :

The Figure (4-7)show that direct or positive correlation between IL-15 and Anti –IgG antibody level , this result might be show that increased IL-15 production may enhancement of antibody production , especially in late infection because the IgG was produced later than cytokines and other antibodies such IgM .

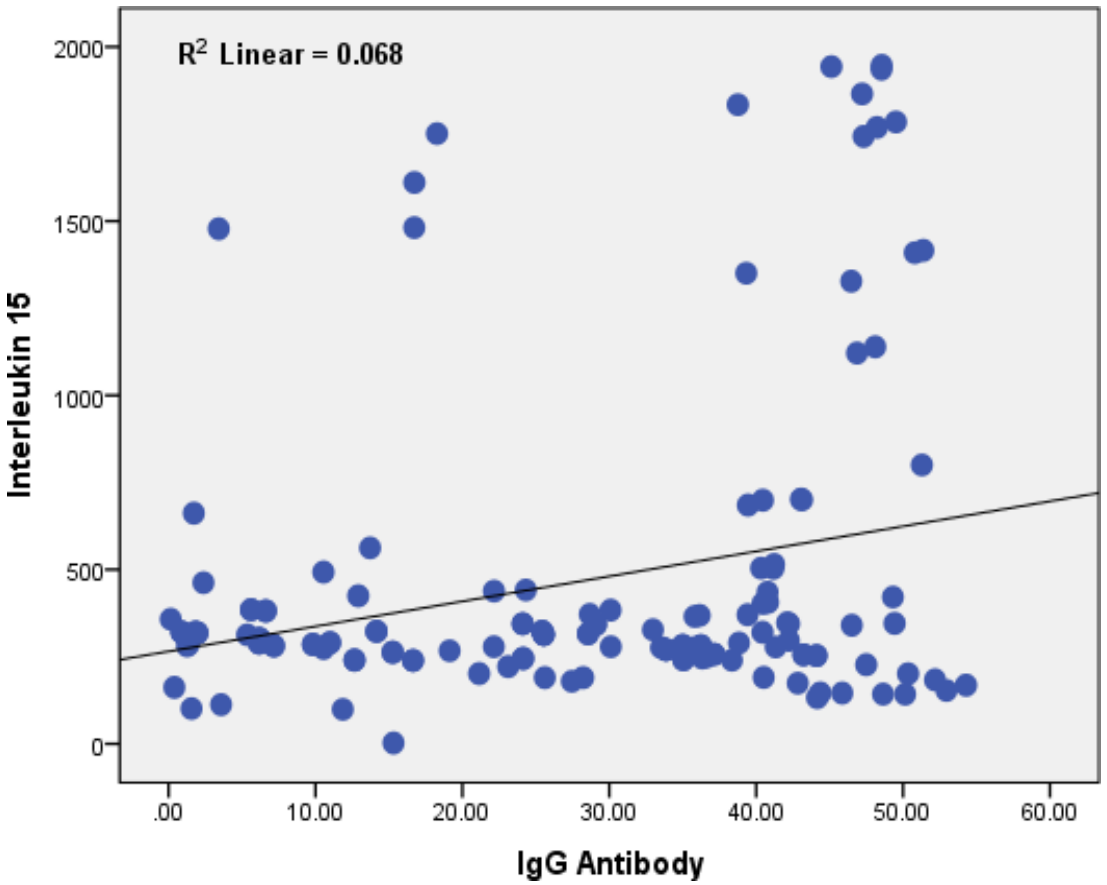


Figure (4-7) Correlation of IL- 15 and Anti -SARS-COV-2 –IgG Antibody among Studied Groups .

4.11.8.Correlation of a INF – γ and anti -SARS-COV-2 IgM Antibody among Studied Groups (Vaccinated) :

As like as IL- 12 , the figure (4 -8) show that indirect or negative correlation between a INF – γ and Anti –IgM antibody level , this result might be show that increased INF – γ production earlear than antibody production or in the first few days of infection while antibody need mre time to produce .

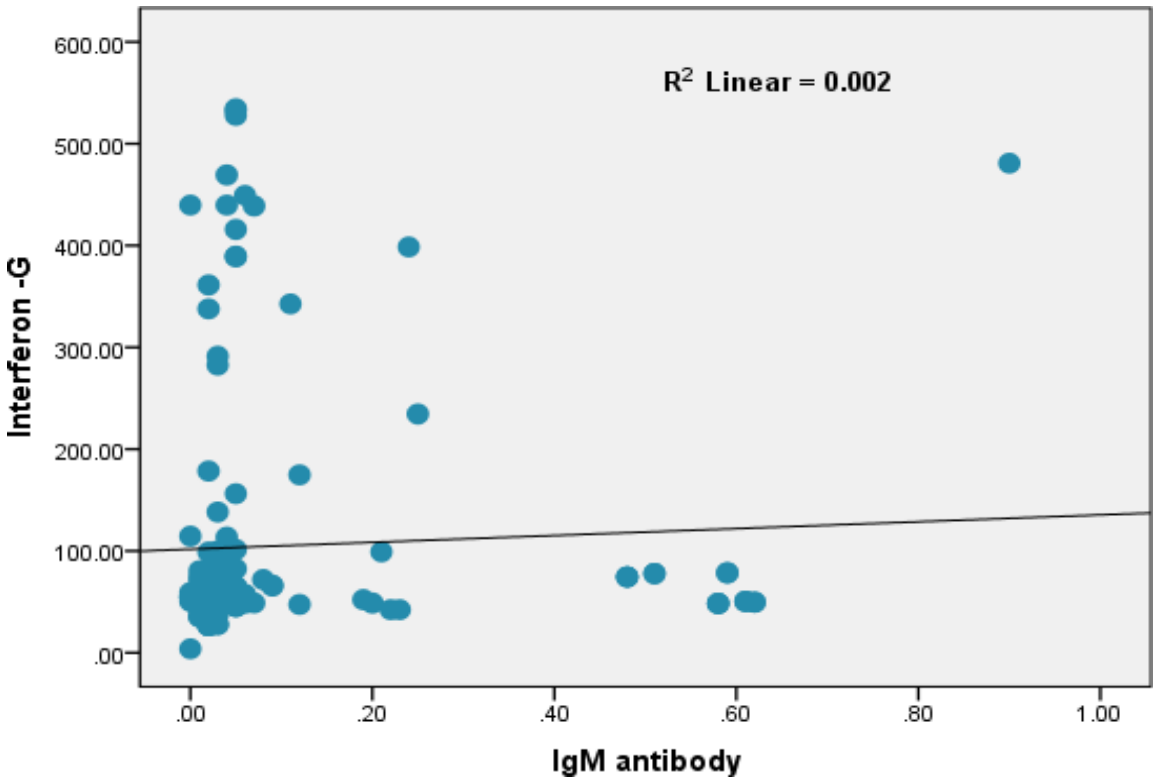


Figure (4-8) Correlation of a INF – γ andA nti -SARS-COV-2 IgM Antibody among Studied Groups.

4.11.9.Correlation of INF – γ and Anti- SARS-COV-2 IgG among studied groups (Vaccinated) :

In the result of figure (4-9) the correlation was show that direct relationship between INF – γ and anti SARS-COV-2 IgG antibody , this result might be indicted that increased of interferon level lead to enhancement of antibody production especially IgG against Sars-Cov 2 virus.

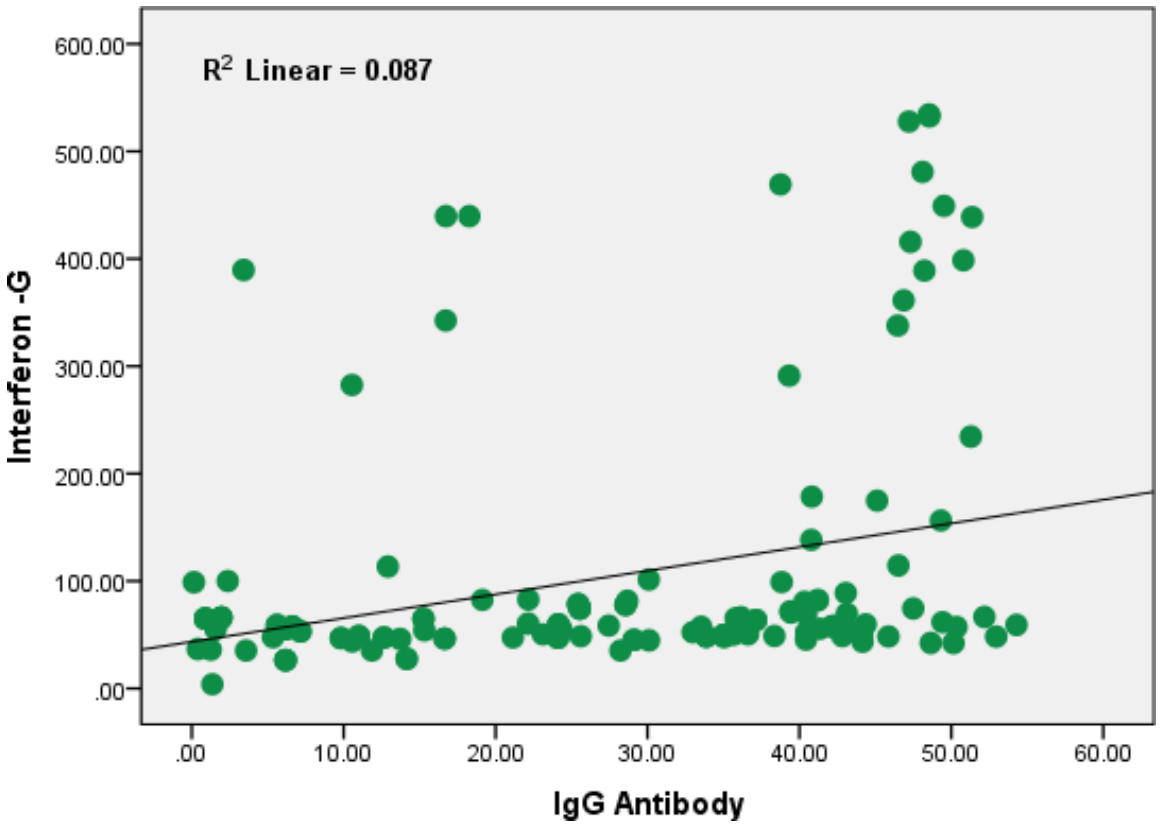


Figure (4-9) Correlation of INF – γ and Anti- SARS-COV-2 IgGamong Studied Groups.

4.11.10.The Correlation between Anti-SARS-COV-2 IgM and IgG Antibodies among Studied Groups (Vaccinated) :

Although the IgG more than IgM , there was a direct correlation between IgM and IgG antibodies against SARS-COV-2 virus among the Vaccinated , curried and healthy population .

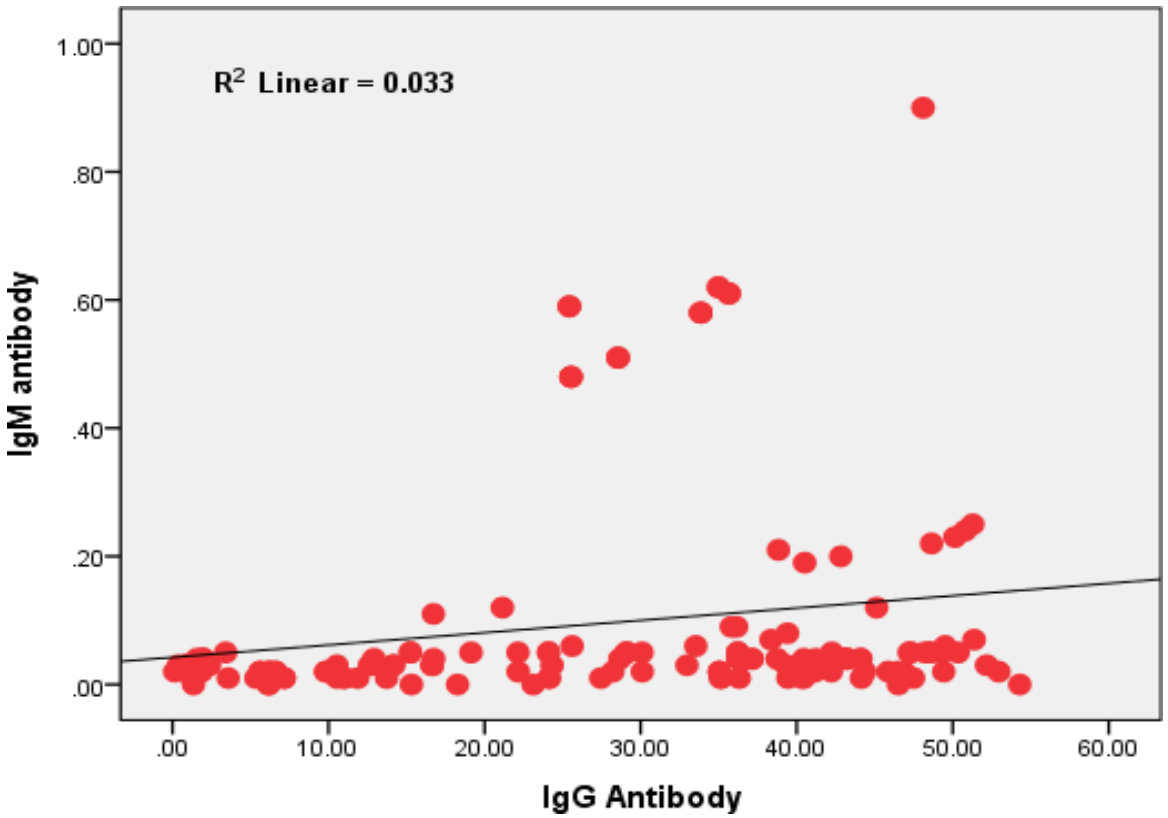


Figure (4-10) The Correlation between Anti- SARS-COV-2 IgM and IgG aAntibodies among Studied Groups.

4.12.Sensitivity and Specificity of Rapid and Quantitative measurement of IgM and IgG:

The Roc curve analysis to determination of sensitivity and specificity between the qualitative or rapid determination of IgM and IgG against Sars- Cov2 virus and quantitative measurement of IgM and IgG levels , the result show that the IgG level have more reliable and specific to monitor of the immune response in vaccinated and control population . The Figure (4-12) and table (4 - 11) show the analysis curve and table of aria under the curve.

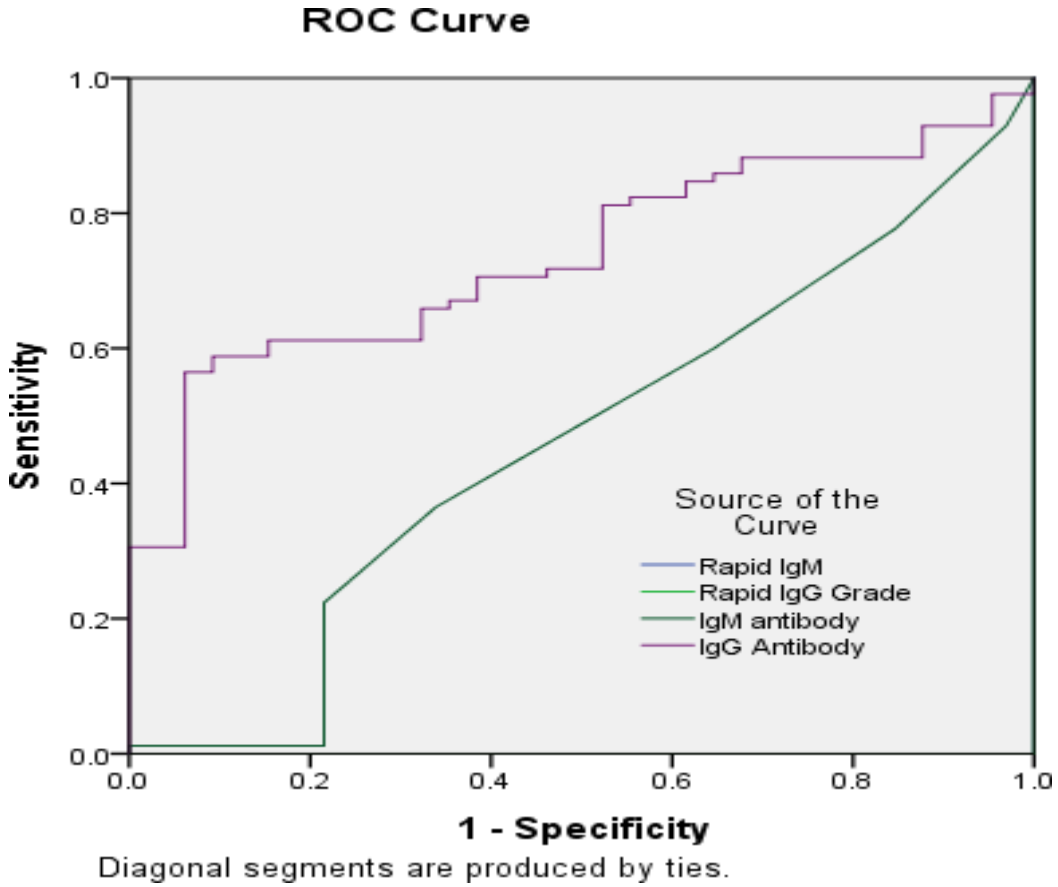


Figure (4-12) Roc Curve of Anti -SARS-COV-2 Measurement

Table (4-11) The Analysis Table of Antibody Measurement

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	ymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Rapid IgM	.000	.000	.000	.000	.000
Rapid IgG Grade	.000	.000	.000	.000	.000
IgM antibody	.459	.048	.396	.366	.553
IgG Antibody	.736	.041	.000	.657	.816
The test result variable(s): IgM antibody has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

Conclusion and Recommendations

Conclusions:

1. Low level of anti SARS-COV-2 –IgM antibodies of both vaccinated and control groups ,while increased of Sars-cov2 –IgG in vaccinated population in comparison with curried patients and healthy control .
2. Highly increased in IL-12, IL-15 and INF - γ levels in comparison with control groups (Curid and healthy).
3. The age groups (20 - 29 years and > 60 years) have higher level of Anti – SARS-COV-2 IgG , the IgM level shows that there is no difference in level after comparison with other age groups as well as control .
4. females have higher level of Anti-SARS-COV-2 IgG antibody rather than male.
5. The smoking population has more induced antibody production than nonsmoking one , while there is no Specific IgM antibody differences between smoking and nonsmoking
6. The cytokines (IL-12 , IL-15 and INF - γ) levels among the infected population after receiving vaccine have higher level than non - infected people and repeated more than one infection , as like as the control groups curried and healthy population, at P Value < 0.05 .
7. Association with qualitative antibody at high IgG score with the quantitative level of the anti- SARS-COV-2 –IgG antibody.

Recommendations:

1.Guiding a study to find the relation ship between interleukins and other immunological parameter with Covid-19 .

2. More studies might be made to investigate other vaccines.

3.Study the relation ship between the Rapid test and Vidas Test to assay other cytokines.

4.Make study molcular to genes that have relation ship with Vaccine.

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الخلاصه:

اجريت هذه الدراسه في محافظة بابل من تشرين الثاني 2021 الى كانون الثاني 2022 على 85 شخص تم تلقيحهم مع او بدون اصابه سابقه كمجموعه اختباريه مقارنه مع 35 شخص مصاب سابقا ومتعافي من مرض كوفيد 19 كمجموعة سيطره موجبه مع 30 من الاشخاص الاصحاء غير المصابين بمرض كوفيد 19 كمجموعة سيطره سالبه اجريت دراسة معايير مختلفه لتقييم الحاله المناعيه بعد تناول الجرعات الكامله من اللقاحات المختلفه.

كان هناك مستوى منخفض من الاجسام المضاده ل كوفيد 19 –اميونوكلوبيولين–M لكل من المجموعه الملقحه والمجموعه غير الملقحه ببينما زادت نسبة كوفيد 19 اميونوكلوبيولين–G في السكان اللذين تم تلقيحهم مقارنة بالمرضى المصابين سابقا وغير المصابين غير الملقحين الانحراف القياسي (14.033.21 + 1606 ,20.36 + 13.77, 21.47)عند مستوى معنويه P.<0.05 قد تشير هذه النتيجه الى ان اللقاح قد يؤدي الى انتاج اميونوكلوبيولين–G بدلا من اميونوكلوبيولين–M عند دراسة تاثير انترلوكين 12وانترلوكين 15 وانترفيرون كاما على عينة الدراسه كان هناك زياده في مستويات انترلوكين 12وانترلوكين 15 وانترفيرون كاما مقارنة بمجموعات السيطره المصابين وغير المصابين انترلوكين12 عند الانحراف (0.95 ± 6.04 ,0.82 ± 6.0 ,4.78 ± 26.24) وانترلوكين15 عند الانحراف القياسي ± 292.80 , 37.06 ± 294.53 , 60.62 ± 596.84) (39.11وانترفيرون كاما عند الانحراف القياسي(12 ± 54.92 , 50.92±143.29 ,54.72 +11.92)على التوالي عندمستوى معنويه P.<0.05

اظهرت نتائج العلاقه بين الفئات العمريه والاجسام المضاده للكوفيد 19 نوع اميونوكلوبيولين–M,G ان الفئات العمريه من 20–29 واكثر من 60 سنه لديها مستوى من مضادات الكوفيد 19 نوع اميونوكلوبيولين–G اظهر مستوى مضادات الاميونوكلوبيولين نوع M انه لايوجد فرق في المستوى بعدالمقارنه مع الفئات الاخرى وكذلك مجموعة السيطره ونتائج الفئات العمريه لجميع الفئات العمريه للبالغين المدروسه اكبر من 60 عاما لديهم مستوى اقل من السايتوكينات بالمقارنه مع الفئات العمريه للشباب والبالغين اللذين لديهم مستوى اعلى.

اظهر البحث ان هناك فرقا بين الانثى التي تم تلقيحها ولديها مستوى اعلى من الاجسام المضاده الاميونوكلوبيولين نوع G مقارنة بالذكور ولم يكن ل الاميونوكلوبيولين نوع M المحدد اختلافات في كل من الذكور والاناث وكذلك عينة السيطره السكان الذكور لديهم مستوى اعلى من السايتوكينات بالمقارنه مع الاناث في المجموعه التي تم تلقيحها ومجموعة السيطره المصابين سابقا وغير المصابين

اظهرت النتيجه ان السكان المدخنين قد تسببو في انتاج اجسام مضاده اكثر من غير المدخنين بينما لايوجد فرق محدد في المضادات من نوع M في جميع حالات التدخين وعدم التدخين في كل من المجموعتين المدروسه والسيطره بينما يظهر مستوى السايتوكينات مرتفع في مجموعات المدخنين عن غير المدخنين وكذلك مع مجموعات السيطره المصابين سابقا وغير المصابين.

اظهرت النتائج ان السكان غير المصابين لديهم مستوى مرتفع من المضادات نوع G مقارنة مع السكان المصابين بينما كان مستوى السايتوكينات بين السكان المصابين بعد تلقي اللقاح اعلى مقارنة بالشخص غير المصاب وتكررت اكثر من اصابه كما هو الحال في المجموعات الضابطه من السكان الاصحاء والمصابين سابقا.

اظهر الاكتشاف السريع للاجسام المضاده G, M للكوفيد 19 وجود جسم مضاد M ايجابي في الناس اللذين تم تلقيحهم واللذين لديهم مستوى عالي من الاجسام المضاده نوع G مقارنة بالناس المصابين وكان هناك ارتباط مع الاجسام المضاده النوعيه عند درجه العاليه المضاد نوع G مع الكميه اظهر مستوى هذا المضاد مستوى تركيز مرتفع مقارنة بالدرجات النوعيه الاخرى للاجسام المضاده نوع G المنخفضه والمتوسطه وكذلك مجموعة السيطره اظهرت نتيجة لقاح فايزر انه يحفز حمايه اكثر من السينوفارم في التفاعل المناعي كان هناك ارتباط مباشر بين السايتوكينات المدروسه وكذلك هناك ارتباط مباشر بين السايتوكينات المدروسه والمضادات نوع G وهناك ارتباط غير مباشر بين مجموعات السايتوكينات المدروسه ومضاد نوع M يستخدم منحني تحليل دقة النتائج لتحديد الحساسيه والنوعي او السريع للاجسام المضاده G, M ضد الكوفيد 19 والقياس الكمي لمستويات للاجسام المضاده G, M.

ظهرت النتيجه ان مستوى المضاد نوع G اكثر موثوقيه وتحديدا لرصد الاستجابه المناعيه في الناس السكان الملقحين والسيطره.

جمهورية العراق
وزارة التعليم العالي و البحث العلمي
جامعة بابل / كلية العلوم للبنات
قسم علوم الحياة

تقييم بعض المعايير المناعيه في الاشخاص الملقحين بلقاحات كورونا في بابل- العراق

الرسالة مقدمة الى
مجلس كلية العلوم – جامعة بابل و هي جزء من متطلبات نيل درجة الماجستير في العلوم
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