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Immune Response in COVID-19: A Review

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The article is modified by included the valuable suggestions of the reviewer(s) listed below:

Revision:

Corrections given by the reviewers	Corrections done
The comments were adressed and the manuscript improved. I suggest change the title. For example "Immune Response in COVID-19: A Review"	Thanks a lot. The title is changed as "Immune Response in COVID-19: A Review" according to the valuable suggestions. The Title is marked br red color.

Immune Response in COVID-19: A Review

Abstract:

The immune system protects us from viruses and diseases. It produces an antibody to kill pathogen. This review shows a brief picture about the immune system to protect us from COVID-19. It illustrates the process of the immune system, how it works, and mechanism of the immune system to fight virus. It also provides information on recent COVID-19 treatment and experimental data. Various types of potential challenges are also discussed for the immunes system. At the end, some foods have been suggested and some are discouraged. Physical exercise is also encouraged. This article can be used as a state of the art at this critical moment to the globe for a promising alternative solutions related to the survival of people from coronavirus.

Keywords Immunity System, COVID-19, Case Study, Potential Challenges, Data Analysis

1. Introduction

The earth is relaxing but human is dying. As of 18th April 2020, more than 154,000 people died, 2.2 million have been affected, and at least 185 countries have been affected by corona virus. The world experienced coronavirus for the first time in 2002-2003 by Severe Acute Respiratory Syndrome(SARS) and in 2011 by Middle East Respiratory Syndrome (MERS). The causative agents for both cases (SARS-CoV and MERS-CoV, respectively) were newly identified coronavirus with zoonotic origin in the genus Beta coronavirus [1]. The present corona virus (SARS-CoV-2) COVID-19 appeared for the first time in Wuhan, China, at the end of 2019. People are being affected by human to human transmission due to close contact [2-3] and people affected by COVID-19 suffer from severe respiratory illness [4]. People who are elderly and have numerous comorbidities are the most vulnerable to this virus [5-6].

Although there is no registered treatment or vaccine for this disease [7] but for the treatment of affected people, limited urgent use of chloroquine and hydroxychloroquine have been approved by the US Food and Drug Administration (FDA). The use of an anti-viral drug called Favilavir as a treatment for coronavirus has been approved by The National Medical

Products Administration of China. The drug has shown efficacy in treating the disease with very low side effects in a clinical trial involving 70 patients. The clinical trial is going on in Shenzhen, Guangdong province [8]. This review article reported the recent observations to develop immunity level in human body for resisting the corona virus as an alternative solution before the invention of any drugs and vaccinations.

2. Process of Immune System in Human Body

Our whole body consists of the organs of the immune system (Figure 1) to protect against diseases [9-10]. It plays a key role to maintain health and pathogenesis. It also protects our body from harmful substances, germs and cell changes (neoplasm) [11].The key player in the immune system is the white blood cells (WBC)which can travel throughout the body using the blood vessels. To monitor for invading microbes, our body exchanges cells and fluids between blood and lymphatic vessels and enables the lymphatic system. The lymphatic vessels carry lymph. Each lymph node contains specialized compartments where they can encounter antigens. Through the incoming lymphatic vessels, the immune cells and foreign particles enter the lymph nodes. When they are in the bloodstream, they are transported to tissues throughout the body. They continue the cycle all over through patrolling for foreign antigens everywhere and then gradually drift back into the lymphatic system. The immune cells gather, work, and serve to confront antigens in lymph nodes and spleen's compartments [12].

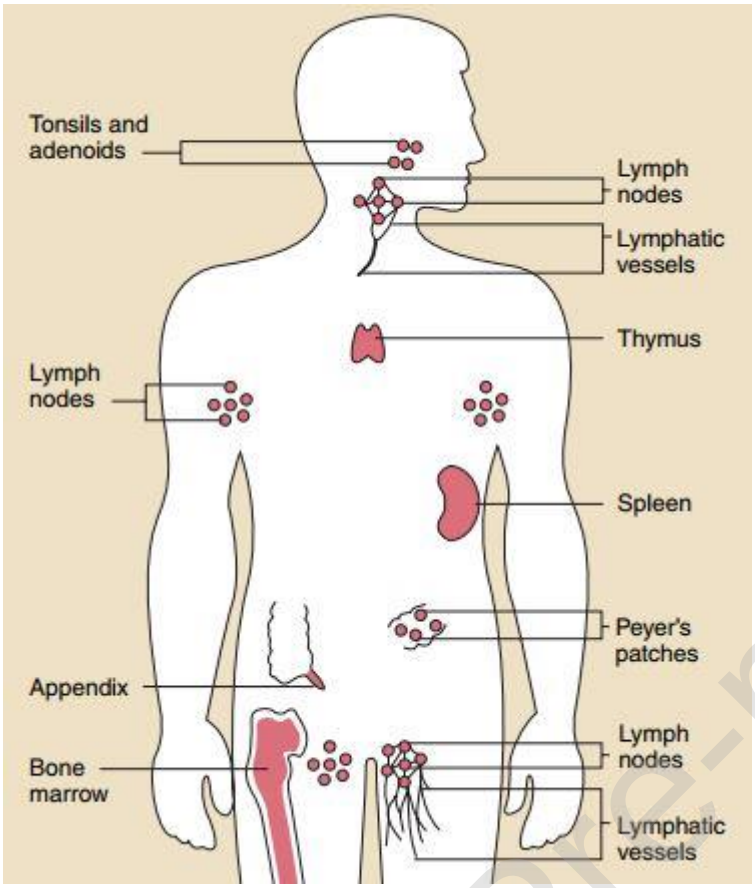


Figure 1: The organs of the immune system are positioned throughout the body [12].

3. Impacts of Covid-19 on Human Body:

COVID-19 is an RNA virus with a crown like appearance. Its diameter is approximately 60-140 nm. On one side, it has a concave surface with a ridge. It makes a larger binding interface ad well as more contacts with ACE2. It can make better contact with the N-terminal helix of ACE2 and have higher affinity [13]. It is transmitted through respiratory droplets from coughing and sneezing. It enters our nasal system by inhaling and starts replicating. ACE2 is the main receptor for the COVID-19 virus [14]. The spike protein present on the surface of COVID-19 gets pinched inside the host cell binding to the ACE2 receptor. Here, the enzyme furin present in the host cell plays a vital role for the virus to enter, which was absent in SARS-CoV [15].Then the virus starts to propagate with limited innate immune response and can be detected by nasal swabs. The virus then propagates and reaches the respiratory tract. There it faces a more robust innate immune response. At this stage, the disease is clinically manifest and an innate response cytokine may be predictive of the subsequent clinical course [16]. For beta and lambda infections, viral infected epithelial cells are a major source [17]. The disease will be mild for 80% of the infected patients and mostly restricted to the upper and conducting airways [18]. With

conservative symptomatic therapy, these individuals may be monitored and monitored at home. Around 20% of the infected patients will develop pulmonary infiltrates and some of these will develop very severe disease [19]. The mortality rate of severe COVID-19 patients can be as high as 49% showed by a recent epidemiological by China CDC [20]. From Wuhan, 292 COVID-19 patients were studied there. Age was the risk factor of severe patients shown by the Lasso algorithm. When the age of severe patients increased by 5, years, the risk increased by 15.15%. Most of the patients with COVD-19 were elderly patients in the severe group with basic diseases. Chronic obstructive pulmonary disease, hypertension, malignant tumor, coronary heart disease, and chronic kidney disease were more frequent in the severe group than in the mild group. From 145 severe cases, 51 patients died, accounting for 34.69% and 90.2% dead patients are over 60 years old. 40 patients had basic disease out of 51 deaths, accounting for 78.43%. Recent reports show that patients with more than 60 years of age and having comorbidities, especially hypertension are believed to be risk factors for severe disease and death from SARS-CoV-2 infection [21-23].

4. Mechanism of Immune Systems in Human Body Against Covid-19

As there is no registered medicine or vaccine against COVID-19, our immune system is the best defense. The immunity system supports our body's natural ability to defend against pathogens which include viruses, bacteria, fungi, protozoan, and worms [24-25], resist infections. As long as the immune system runs smoothly, we do not notice infections like COVID-19. Our immune system can be categorized into three categories. They are, namely, innate immunity (rapid response), adaptive immunity (slow response), and passive immunity (Figure 2). Passive immunity is again two types and they are natural immunity which we receive from our mother and artificial immunity that we receive from medicine. Skin and inflammatory response begins when our body is affected [26-27]. However, when our body encounters any germs or viruses for the first time, the immune system cannot work properly and we become sick. The same thing has happened in the case of COVID-19 [28].

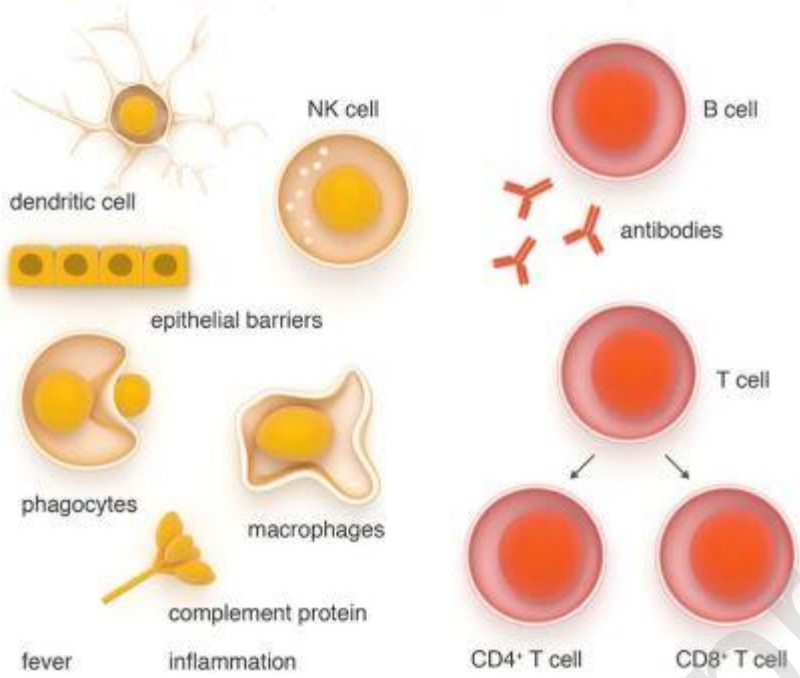


Figure 2: Innate and Adaptive immune system [28].

When the cells of the immune system become educated, it completes its jobs by recirculating between central and peripheral lymphoid organs and migrating it and from sites of injury via blood (Figure 3). Blood carries naïve and educated immune cells from one site to another, as it flows throughout the body, it acts as a pipeline for the immune system. The cells again enter into the bloodstream to be transported to tissues throughout the body after exiting these nodes through outgoing lymphatic vessels [29].

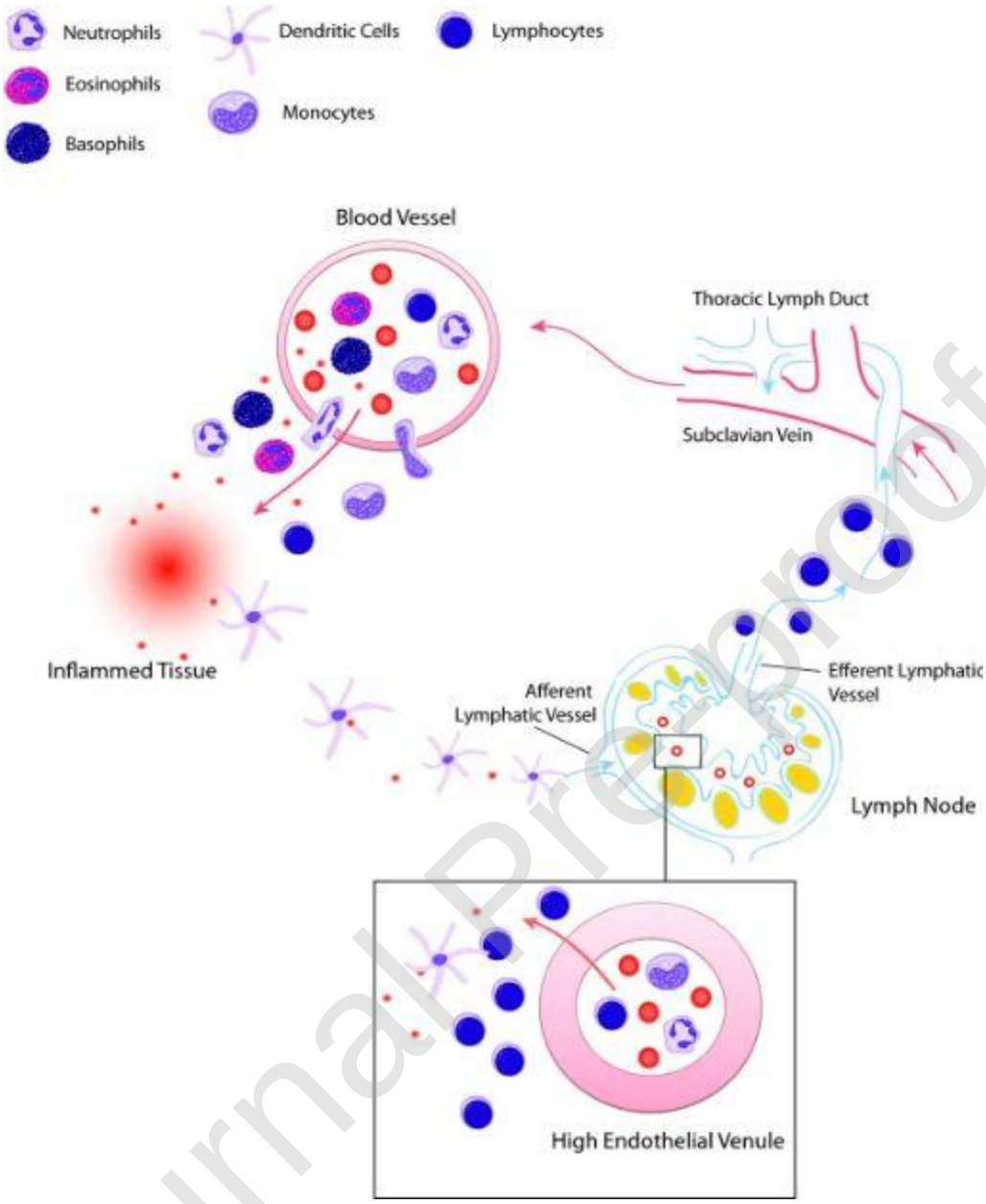


Figure 3: Blood in the pipeline of the immune system [29].

Many molecular and cellular profiling assays are now abundant for the study of the human immune system (Figure 4). The level of advancement of instruments has happened such as polychromatic flow cytometers have improved over the past few years. In the fields of genomics and proteomics, major technological breakthroughs have also happened, thus creating today a unique facility for the study of human beings in health and disease where inherent heterogeneity dictates that large collections of samples be analyzed [29].

After being affected by virus immune responses to mediate antibody. The B cells are assisted by T cells to differentiate into plasma cells, which in return produce antibodies specific to a viral antigen. Neutralizing nature antibody is efficient in fully blocking the virus from entering into host cells to limit the infection and plays a very intense protective role at the later stage of infection and prevents relapse of infection in the future. In contrast, a cellular immunity response can be seen inside the infected cells, which is mediated by T-lymphocytes. The overall adaptive immune response is directed by helper T cells, while cytotoxic T cells play a vital role in the clearance and cleaning of viral infected cells [30].

Information from SARS-CoV and MERS CoV may allow exploration of knowledge to understand how SARS-CoV-2 escapes the host's immune response as data on SARS-CoV-2 are still very few. 80% RNA sequence of SARS-CoV and 50% of RNA sequence of MERS-CoV matches with the RNA of SARS-CoV-2 [31] and SARS-CoV-2 exhibit additional genomic regions. Compared to SARS-CoV and other closely related coronaviruses, its spike protein is 20-30 amino acids longer. Thus, SARS-CoV-2 has similar immune evasion strategies, but an additional mechanism is still undiscovered [32-33].

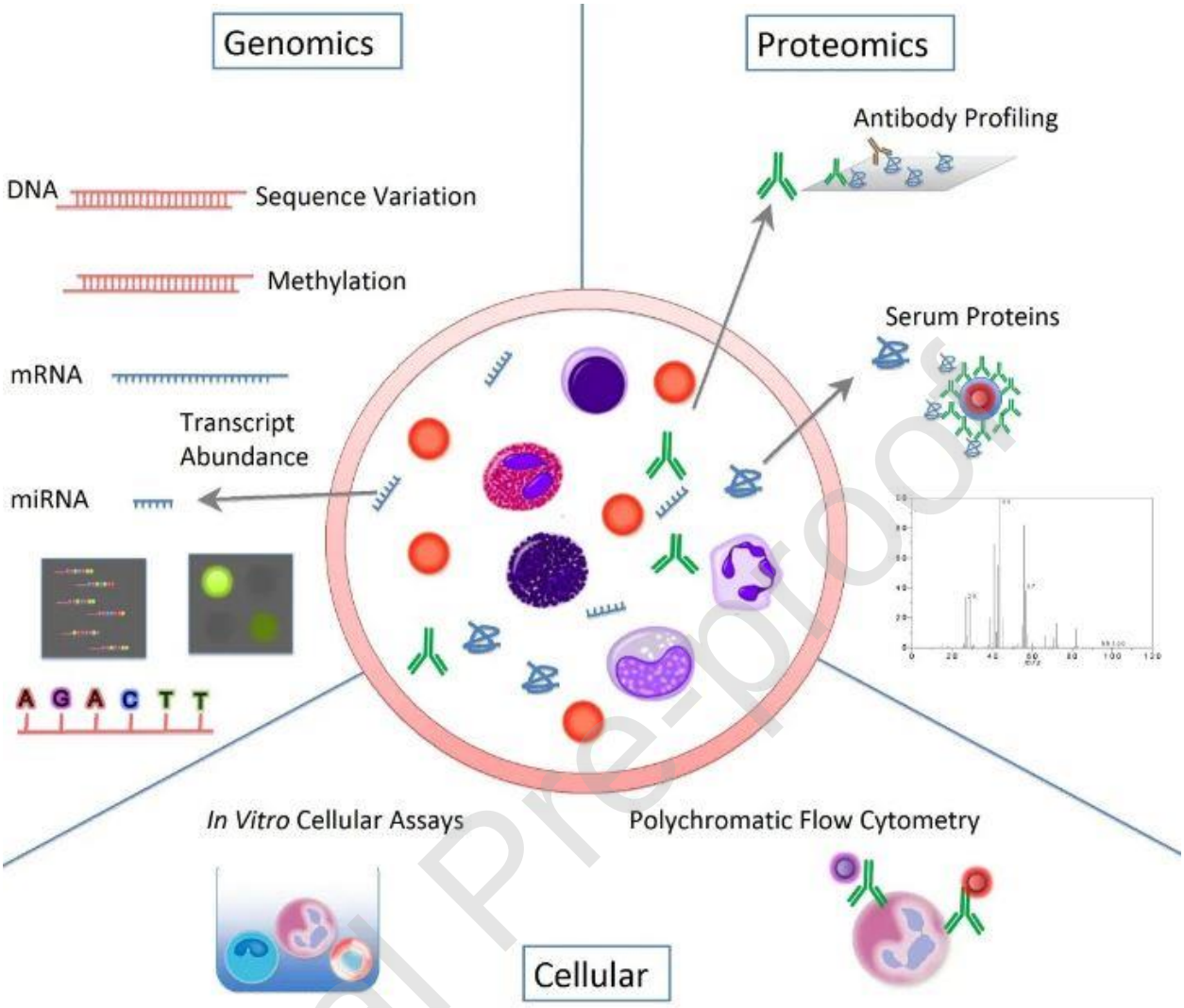


Figure 4: The immune profiling armamentarium [29].

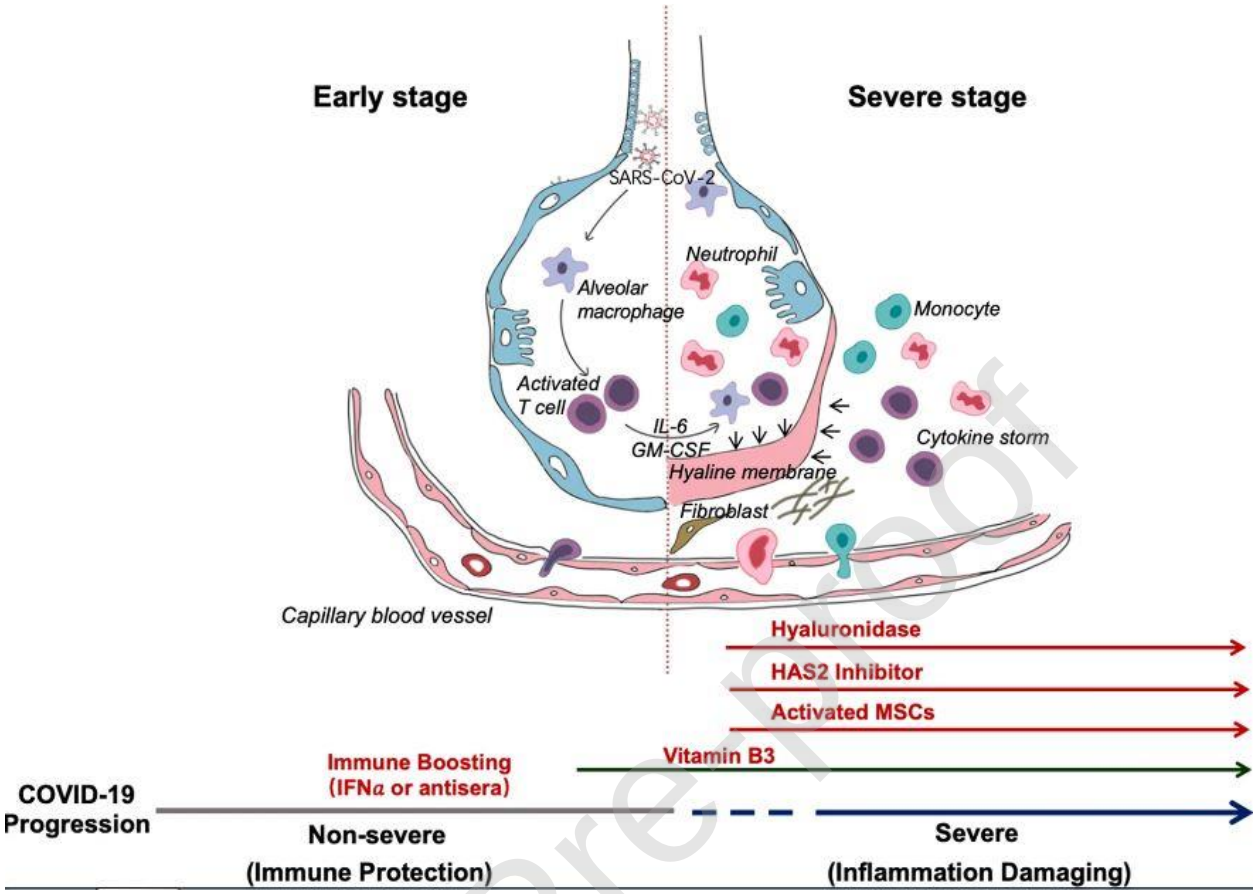


Figure 5: Schematic representation of the progression of COVID-19 infection and potential adjuvant interventions [34].

According to Yufang Shi et al. [34] overall, the synopsis is based on some clinical common sense. They proposed some normal approaches to the treatment of COVID-19 patients (Figure 5). They believed that the two-phase immune defense-based protective phase and inflammation-driven damaging phase division are essential. During the first, Doctors should try to boost immune response and in the second phase suppressing it. Vitamin B3 should be used just after the coughing begins as it is highly lung protective. When breathing difficulty starts, hyaluronidase can be given intratracheally and at the same time 4-MU can be used to inhibit HAS2. Clearly, susceptibility information will be provided by HLA typing for strategizing prevention, treatment, vaccination, and clinical approaches.

5. Reasons of Failure:

The leading cause for mortality of COVID-19 patients is respiratory failure from acute respiratory distress syndrome [35]. Secondary haemophagocytic lymphohistiocytosis (sHLH) is characterised by fulminant and fatal hypercytokinaemia with multiorgan failure and it is under recognized. Viral infection triggers sHLH and occurs in 3·7–4·3% of sepsis cases in adults [36-37]. sHLH, resembled by a cytokine profile, is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, interferon-γ inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, monocyte chemoattractant protein 1, and tumour necrosis factor-α (TNF-α) [38]. A recent retrospective fatality predictor's multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin and IL-6, suggesting that mortality might because of virally driven hyper inflammation [39].

6. Treatment for COVID-19 Patients:

Research is going on around the world to develop a vaccine against COVID-19. According to report [40], 115 vaccine candidates are on the project. Among them, 78 are confirmed as active and 37 are unconfirmed. 73 are at exploratory stage out of 78 confirmed active projects. The most advance candidates have been moved into clinical development. The below-1table shows the clinical phase vaccine candidates for COVID-19.

Candidate	Vaccine characteristic	Lead developer	status
mRNA-1273	LNP-encapsulated mRNA vaccine encoding S protein	Moderna	Phase I (NCT04283461)
Ad5-nCoV	Adenovirus type 5 vector that expresses S protein	CanSino Biologicals	Phase I (NCT04313127)
INO-4800	DNA plasmid encoding S protein delivered by electroporation	Inovio Pharmaceuticals	Phase I (NCT04336410)
LV-SMENP-DC	DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs	Shenzhen Geno-Immune Medical Institute	Phase I (NCT04276896)

Pathogen-specific aAPC	aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	Shenzhen Geno-Immune Medical Institute	Phase I (NCT04299724)

Table 1: Clinical phase vaccine candidates for COVID-19 [40].

According to another report [41], 108 adults have received a low, middle, or high dose of the vaccine, given as an intramuscular injection. All of them were not affected by SARS-CoV-2 and their age was in between 18 to 90 years. Their mean age was 36.3 and 51% of them were male and observed 28 days. Live virus or pseudovirus neutralisation assays can detect neutralizing antibodies, in addition to binding antibodies measured by ELISA at around 14 days. At 28 days, dose dependent antibody responses peaked with seroconversion documented in 50-75% of participants in the middle and high dose groups. Moreover, specific T-cell responses toward the spike glycoprotein were shown by interferon γ enzyme-linked immunospot, and flow-cytometry. Among 83-97% participants, dose dependent responses were detectable starting from 14 days. The most common adverse effects were fever, fatigue, headache, and muscle pain. Study shows that [42] for the treatment of COVID-19, convalescent plasma therapy is effective. The survival rate of patients with severe acute respiratory syndrome of viral etiology has been improved treatment [43]. Pre-donation assessment is performed to ensure compliance with current regulations of plasma donors [44]. Those who have recovered, not infected by COVID-19 for the last 14 days, age in between 18 to 65 are the subject of convalescent donors. Those who are from the tropical disease area are also excluded. Plasma is collected at around 400-800 mL form each donors and stored in units of 200 or 250 mL, frozen within 24h of collection to be used for further transfusions [45]. The safety of using convalescent plasma is another issue. Any adverse event did not associate during the epidemic of Influenza, SARS-CoV and MARS-CoV except Ebola. Reports say treatment with convalescent plasma for COVID-19 patients is safe without any major adverse events [46]. The below-2 table shows the associate adverse events to convalescent plasma in different epidemics.

Country	Viral etiology	Adverse events	References
China	COVID-19	none	[47]

China	COVID-19	none	[48]
China	COVID-19	Self-limited facial erythema in 2/10 patients. No major adverse events.	[49]
China	COVID-19	none	[50]
South Korea	COVID-19	none	[51]
China	SARS-CoV	none	[52]
China	SARS-CoV	none	[53]
China	SARS-CoV	none	[54]
Taiwan	SARS-CoV	none	[55]
China	SARS-CoV	none	[56]
China	SARS-CoV	none	[57]
China	SARS-CoV	none	[58]
South Korea	MERS-CoV	none	[59]
Guinea	Ebola	Nausea, skin erythema, fever. No major adverse events.	[60]
China	Influenza A (H1N1)	none	[61]
China	Influenza A (H1N1)	none	[62]
China	Influenza A (H1N1)	none	[63]
China	Influenza A (H1N1)	none	[64]

Table 2: Associated adverse events to convalescent plasma in different epidemics.

As there is no definite and specific treatment for the COVID-19 patients, some antiviral agents are prescribed to the patients depending the condition and location of the patients. Among the antiviral agents, Remdesivir is the most popular potential drug for the treatment of COVID-19 patients. For the treatment of Ebola virus infection in 2017, Gilead Sciences synthesized and developed it and it is a phosphoramidate prodrug of an adenosine C-

nucleoside and a broad-spectrum antiviral agent [65]. Hydroxychloroquine and Chloroquine are other drugs that have a long history of clinical use with similar chemical structures often used for the treatment of malaria erythematosus and rheumatoid arthritis [66]. Lopinavir is another one which was administered and marketed in combination with ritonavir by Abbott under the brand name Kaletra in 2000. It is a protease inhibitor with high specificity with HIV-1 protease [67]. Besides, Umifenovir was first developed in Russia and used by both Russia and China for the treatment of prophylaxis, infections associated with influenza A and B and other arbovirus [68]. Favipiravir has been developed by Fujifilm Toyama Chemical, Japan, in 2014 for treating avian influenza resistant to neuraminidase inhibitors [69]. Oseltamivir is used for the treatment of influenza A and B. It targets the neuraminidase distributed on the surface of the influenza virus to inhibit the spread of the influenza virus in the human body [70-72]. The below-3 table shows the off level drugs against SARS-CoV-2 and COVID-19.

Drug	Class	Target	Dosage	References
Camostat mesilate	Serine protease inhibitor	TMPRSS2	200 mg three times daily, for 2 weeks, per oral	[73-74]
Nafamostat mesilate	Serine protease inhibitor	TMPRSS2	240 mg daily, for 5 days, per oral	[75-77]
Chloroquine phosphate	Antimalarial drug	ACE2	250 mg daily until clinical convalescence, per oral	[78-79]
Hydroxychloroquine	Antimalarial drug	Endosome, pH elevation	400 mg loading dose twice daily at day 1, 200 mg twice daily for 4 days, or 600 mg for 6 days, or 400 mg for 5 days, per oral	[80-82]
Remdesivir	Antiviral drug	RdRp	200 mg loading dose at day 1, 100 mg for 9−13	[83-85]

			days, per oral or intravenous	
Lopinavir/ritonavir	Antiviral drug	Viral proteases	400 mg lopinavir and 100 mg ritonavir twice daily, for 14 days, per oral	[86-88]
Umifenovir	Antiviral drug	Membrane fusion, clathrin-mediated endocytosis	400 mg three times daily, for 9 days, per oral	[89-90]
Favipiravir	Antiviral drug	RdRp	6000 mg loading dose at day 1, 2, 400 mg for days 2−10, per oral	[91]

Table 3: Off-label drugs against SARS-CoV-2 and COVID-19 disease [92].

7. Recent Observations for COVID-19 Treatment Improving Immune System: Case Study

The researchers are researching to improve the immune system against COVID-19 and here some of the data are reviewed. 10 proteins are encoded by COVID-19 genome. One of them is the spike protein (S-protein) mentioned as a glycoprotein exists in the virus infected region (Figure 6). The S-protein is a significant therapeutic target, ensured its location, and targetable using antibodies [93]. The formation of neutralizing antibodies immunization of animals with S-protein oriented vaccines is very effective in preventing infection by homologous coronavirus [94]. If human cells are infected by virus entities, epitopes from any of that viruses' proteins can theoretically be bound and presented by MHC-1 receptors on host cell surfaces that lead to stimulation of CD4 and CD8 T cells to provoke antibody-mediated and cell-mediated immune responses.

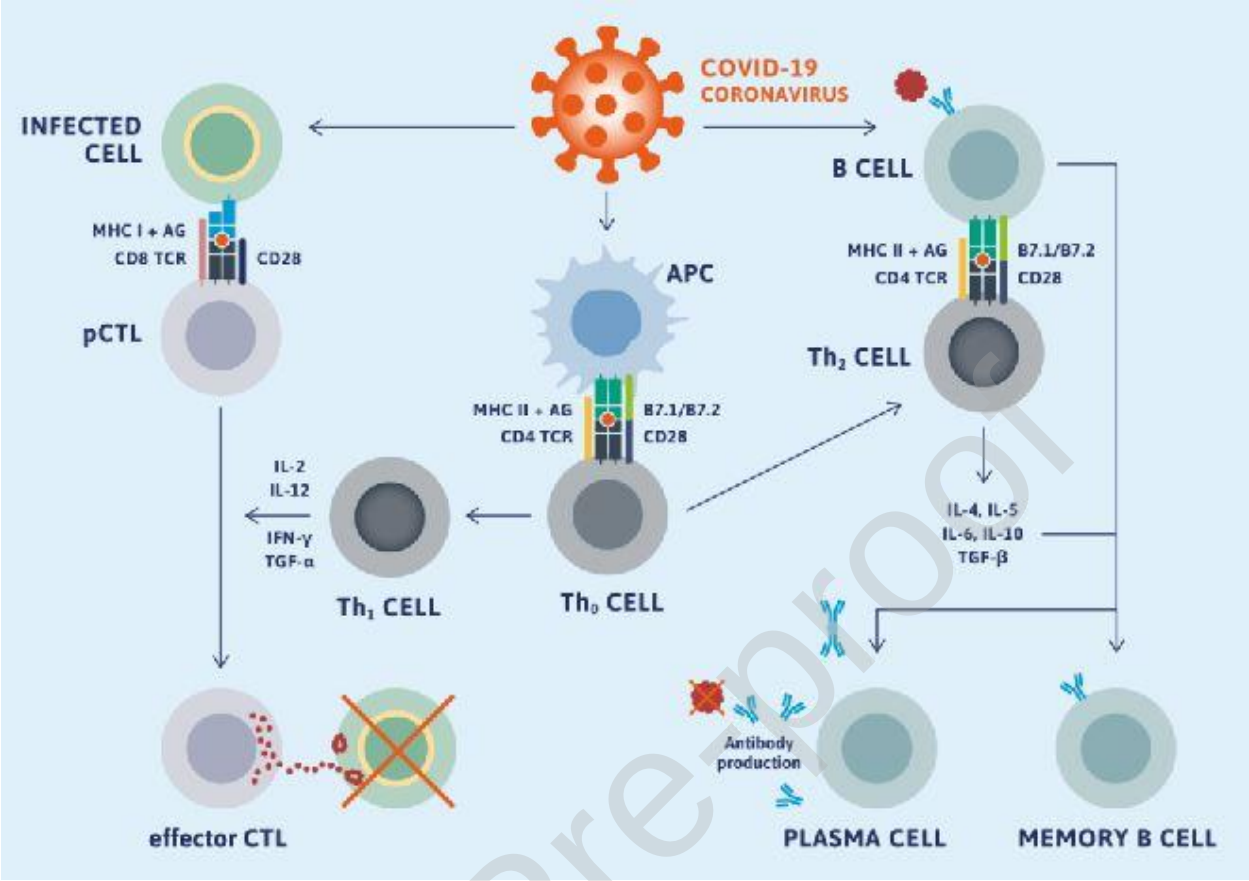


Figure 6: Adaptive immune response against coronavirus requires stimulation of B cell and T cell epitopes [95].

4.1 Case Study-1

In a research at the University of Copenhagen, researchers used net MHC to make in silicon predictions of epitopes presented by 11 MHC-1 alleles that covered approx. 90% of the Asian population. Using that approach, they compiled a list of 100 candidate epitopes for the following MHC alleles: A*0101, A*0201, A*0301, A*11:01, A*2402, B*40:01, C*0401, C*0701, C*0702 and DRB1*0401, resulting in 1,100 MHC/peptide binding studies. For the project, they partnered with Intavis and Intavis synthesized the COVID-19 epitopes assessed in the study. Using their unique Neoscreen technology, they performed in vitro binding studies of epitopes. The study identifies 159 epitopes that stably bind MHC-1 allele and 22 that bind the tested MHC-II alleles [95]. The relevant data is listed in Table 4 and Table 5.

Allele	#	Sequence	Reference
A*0101	309	VTEHDTLLY	[96]
A*0201	42	VLDFAPPGA	
A*0301	52	AVAHKVHLMYK	[97]
A*1101	315	AVFDRKSDAK	[98]
A*2402	288	AYAQKIFKIL	[99]
B*4001	417	REDQWCGSL	[100]
C*0102	369	QYDPVAALF	[101]
C*0401	369	QYDPVAALF	[102]
C*0701	211	YLHARLREL	
C*0702	70	NYFNRMFHF	
DRB1*0401	139	AKFVAAWTLKAAA	[103]

Table 4: reference peptides

	min 60% hits	Enrichment factor
A*0101	14	2.1
A*0201	15	6.1
A*0301	41	1.8
A*1101	49	1.4
A*2402	30	1.5
B*4001	30	1.6
C*0102	3	31
C*0401	1	ND
C*0701	3	5.3
C*0702	3	16
DRB1*0401	22	4.2

Table 5: Number of epitopes with minimum 60 % stability [95].

4.2 Case Study-2 [105]

As of 13 March 2020, outside China, there were 32 countries with more than 100 COVID-19 cases [104]. The highest number of infections was found in seven countries and they were: the United States (n=2294), France (n=3671), Germany (n=3675), Spain (n=5232), Korea (n=8086), Iran (n=11,364), and Italy (n=17,660). The number of

confirmed cases in other countries 25 countries has been found less than 1200 [105]. The related data is noted in Table 3.

The change of R_0 and R_t is connected to the proportion of individuals those have immunity in their body to that pathogen in that population. The alternative method of estimating R_t for a pathogen including the population is by multiplying R_0 through the proportion of that population those are considered non-immune to that pathogen. In this perception, R_0 will only similar level of R_t if there are no immune persons in the population. It indicates that any partial pre-existing immunity to the infecting elements is able to decrease the number of expected secondary cases emerging.

Whenever this perception is applied in case of herd immunity to control the COVID-19 epidemic, the fatality rate of corona virus is in the range between 0.25–3.0% of the estimated population, the measured number of people who may die from affecting this virus, but when the population attains the P_{crit} herd immunity level, can be difficult to accept.

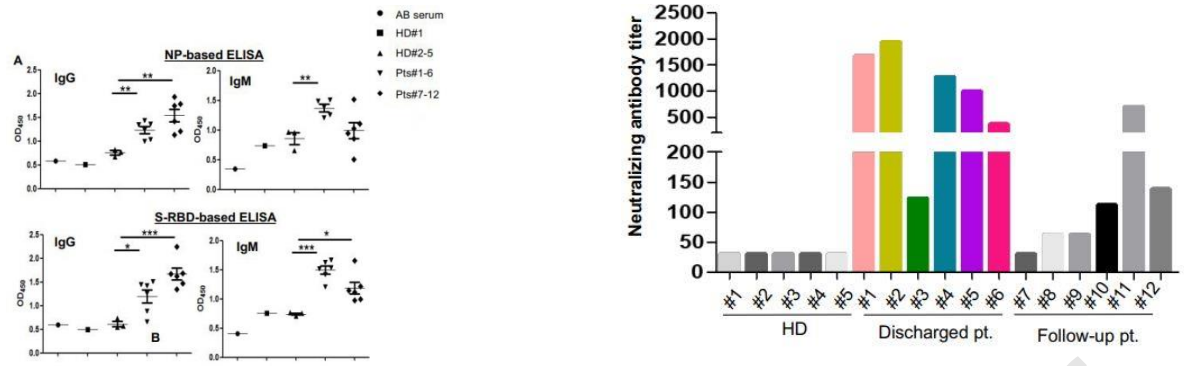
Study countries	**Population infected by COVID-19**	**Estimates of effective reproduction number (R_t) (95% CI), ($n = 32$)**	**Minimum proportion (%) of total population required to recover from COVID-19 to confer immunity (P_{crit})**
R_t >4			
Bahrain	210	6.64 (5.20, 8.61)	85.0
Slovenia	141	6.38 (4.91, 8.38)	84.3
Qatar	320	5.38 (4.59, 6.34)	81.4
Spain	5232	5.17 (4.98, 5.37)	80.7
Denmark	804	5.08 (4.60, 5.62)	80.3
Finland	155	4.52 (3.72, 5.56)	77.9
R_t (2–4)			
Austria	504	3.97 (3.56, 4.42)	74.8
Norway	996	3.74 (3.47, 4.04)	73.3

Study countries	Population infected by COVID-19	Estimates of effective reproduction number (R_t) (95% CI), ($n = 32$)	Minimum proportion (%) of total population required to recover from COVID-19 to confer immunity (P_{crit})
Portugal	112	3.68 (2.86, 4.75)	72.8
Czech Republic	141	3.57 (2.88, 4.45)	72.0
Sweden	814	3.44 (3.20, 3.71)	70.9
The United States	2294	3.29 (3.15, 3.43)	69.6
Germany	3675	3.29 (3.18, 3.40)	69.6
Switzerland	1139	3.26 (3.05, 4.78)	69.3
Brazil	151	3.26 (2.99, 3.55)	69.3
Netherlands	804	3.25 (3.02, 3.51)	69.2
Greece	190	3.12 (2.67, 3.67)	67.9
France	3661	3.09 (2.99, 3.19)	67.6
Israel	143	3.02 (2.56, 3.59)	66.9
The United Kingdom	798	2.90 (2.72, 3.10)	65.5
Italy	17,660	2.44 (2.41, 2.47)	59.0
Canada	198	2.30 (2.07, 2.57)	56.5
Iceland	134	2.28 (1.90, 2.75)	56.1
Rt (1–2)			
Iran	11,364	2.00 (1.96, 2.03)	50.0
Australia	199	1.86 (1.71, 2.03)	46.2
Belgium	559	1.75 (1.55, 1.97)	42.9
Malaysia	197	1.74 (1.61, 1.88)	42.5
Iraq	101	1.67 (1.41,1.97)	40.1
Japan	734	1.49 (1.44, 1.54)	32.9
Korea	8086	1.43 (1.42, 1.45)	30.1
Singapore	200	1.13 (1.06, 1.19)	11.5
Kuwait	100	1.06 (0.89, 1.26)	5.66

Table 6: Estimates of SARS-CoV-2 effective reproduction number (Rt) of 32 study countries (as of 13 March 2020), and the minimum proportion (Pcrit, as% of population) needed to have recovered from COVID-19 with subsequent immunity, to halt the epidemic in that population. [105].

4.3 Case Study-3

Ling, Ni et al. [106] experimented patients with various methods. Initially they used sera but no significant result observed. Then the team focused on NP and S-RBD. To determine optical dilutions, the serum from a patient and human AB serum were titrated. For IgM a dilution of 1:50 and for IgG a dilution of 1:150 were used. Compared with healthy donor groups, NP- and S-RBD-specific IgM and IgG antibodies were both detected in the area of newly discharged patients (Figure 7). When compared with healthy donors, Anti-SARS-CoV-2 IgG antibodies were also more clearly observed than IgM in the follow-up patients. These findings clearly indicate that COVID-19 patients mounted IgG and IgM responses to SARS-CoV-2 proteins, especially NP and S-RBD, and suggest that infected patients could maintain their IgG levels, at least for two weeks. As the RBD domain of the S protein has been shown to bind to the human receptor ACE2, the existence of antibodies against it may suggest neutralization of SARS-CoV-2 infection. To assess that, they performed a pseudovirus particle-based neutralization assay. Patients #1, 2, 4, and 5, all within the discharged group, had high levels of neutralizing antibody titers. Those findings demonstrate that most recently discharged patients had protective humoral immunity to SARS-CoV-2. All except patient #11, the follow-up patients had lower levels of neutralizing antibody titers than recently discharged other patients, although all positive except for patient #7 being negative.



(a) (b)

Figure 7: Detection of antibody responses to recombinant SARS-CoV-2 proteins in COVID-19 patients (A) Serological responses of 12 COVID-19 patients to recombinant NP (top) and S-RBD (bottom). The experiment was performed in duplicate. (B) Measurement of neutralizing antibody titers by pseudovirus-based assay. The experiment was performed in triplicate. NP, nucleocapsid protein. S-RBD receptor binding domain of spike protein. HD, healthy donor. Pt, patient. HD#1, serum was collected in 2018. HD#2-4, the sera were from close contact. *P<**P [106].

8. Potential Challenges in Immune System Development

An effective immune system must have the ability to interpret changes in the world around it and respond properly. However, it faces some challenges to work in different environments with different pathogens (Figure 8). Most of the time it encounters something new considers harmless, but in some cases that can be dangerous. An efficient immune system must have the ability to distinguish this. It should have the ability to adopt in strange environmental changes to fight against infections. A healthy immune system lives happily with a symbiotic microbial farms and reacts when there is a harmful infection. When pathogens enter into our body, it seeks to live inside our body and our cells, the immune system poses many threats. Different door is used for every infection into the cell and blocking off these routes of entry can stop an infection before it begins. The immune system neutralizes an infection by producing antibody. However, this carried out at the proper time. An immune system must stop an infection in its track, before it has established a foothold in the body [107-111].

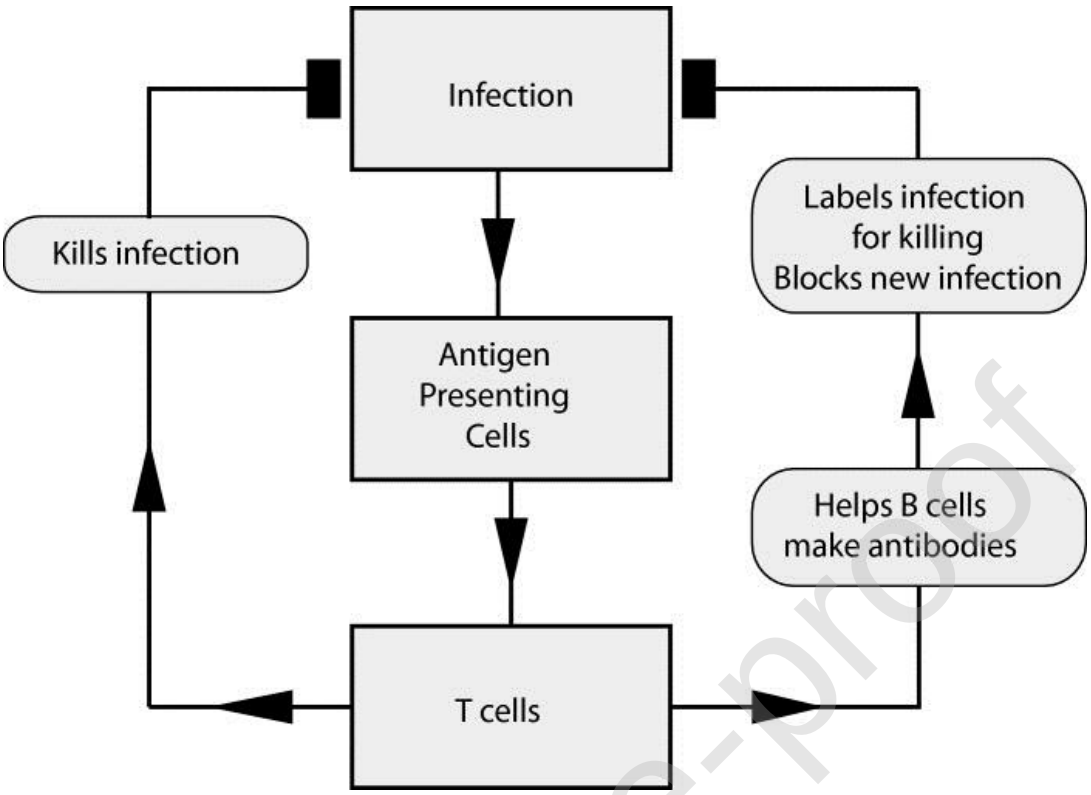


Figure 8: The adaptive immune response to infection [111].

9. Suggested Food, Vaccination, Drugs and Supplementary for Immunity System for COVID-19

According to the World Health Organization, healthy foods as well as hydration are vital. People consuming a well balanced diet are healthier with a strong immune system and have less risk of chronic illness, infectious diseases. The importance of vitamin and mineral is vital. Vitamin B, which is insoluble in water, protects from infection. Vitamin C protects us from flu like symptoms [112]. Lack of vitamin D and E can lead us to infection of coronavirus [113] but vitamin D can be found in sunlight and vitamin E can be found in oil, seeds, fruits, etc. Lack of iron and excess iron can lead to risk [114-115]. Zinc is necessary for maintaining our immune system [116]. Food rich in protein should be on the top priority because it has immune properties (immunoglobulin production) and potential antiviral activity [117-119]. Therefore, in regular meal, people should eat fruits, vegetables, legumes, nuts, whole grains, and foods from animal sources (Figure 9). Food found from plant containing vitamin A should be consumed. 8-10 cups of water should be drunk every

day. Malnutrition is dangerous for COVID-19 patients and proper nutrition should be provided [120-121]. Fruit juice, tea, and coffee can also be consumed. Much caffeine, sweetened fruit juices, fruit juice concentrates, syrups, fizzy, and still drinks must be avoided. Unsaturated fats, white meats, and fish containing low fat are advised to consume. Saturated fat, red meat, more than 5g salt per day, and industry processed food should be avoided [122]. Along with diet, physical activity is another factor. People should be active and do physical exercise regularly to boost the immune system and should have proper sleep [123]. Although there is no registered medicine for COVID-19 treatment but hydroxychloroquine and remdesivir are prescribed which are partially effective [124].

Figure 9: Nutrition advice for adults during the COVID-19 outbreak [122].

10.Conclusions

This review on boosting up the immunity system appears a potential resource for the treatment of COVID-19 patients. The process and mechanism of immunity system can be a good source of knowledge for immunity system development. Recent observations for COVID-19 treatment can be focused on. If potential challenges can be overcome, it can be a great

achievement. Finally, the suggested food should be consumed to boost up the immunity system as there is no registered medicine for COVID-19 treatment.

Conflicts of interest

The authors declared that there is no any conflict of interest

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