Immunometabolism during COVID-19 Infections concerning Pre and Post Vaccination Studies

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***Abstract*- The spread of this COVID-19 is fastidious and it spread all over the globe increasingly in a short period. It is a novel pathogen for humans. There is a need of studying effective treatment and prevention to overcome the pandemic situation due to the COVID-19 virus. In concern to COVID-19 or (SARS-CoV-2) infection, immunometabolism triggers activation of the immune system after Covid-19 infection. In this article, we focused on various immunometabolism activity that occurs from the beginning of infection to the changes that occur after vaccination. We also focus on comorbidities and their effect on increasing the risk of COVID-19 virus infection. This study also represents the worldwide distribution and uptake of different vaccines.**

***Index Terns*- Immunometabolism, Spike proteins, Comorbidities, Vaccines, SARS-CoV-2, Memory cells**

INTRODUCTION

All the living ecosystem of the globe is affected and to the shut-down situation by the novel virus name Coronavirus also known as COVID-19 Disease. [1] This virus can be also known as the (SARS-CoV-2) Severe acute respiratory syndrome Coronaviruses -2. We all know the beginning of this catastrophic virus is from the Huanan Seafood market, Wuhan, Hubei, China in late December 2019. [2] The spread of this COVID-19 is fastidious and it spread all over the globe increasingly in a short period. After findings of different research and its genomic analysis, the primary conclusion of this origin of viruses is very similar to the SARS-CoV-1 and MERS-CoV (Middle East Respiratory Syndrome) generally originated from a bat. This Confirms the Preliminary Reservoir of the virus is the bat.

When the first incidence of COVID-19 was discovered in the Wuhan market in December 2019, the fundamental Spread chronology of the disease began. So, most of the people who have an infection of COVID 19 is having a travel history to the Wuhan market. So, the infectivity Spread of this infection was increased in China and they communicated to the globe about the covid 19 outbreak on December 31st, 2019.

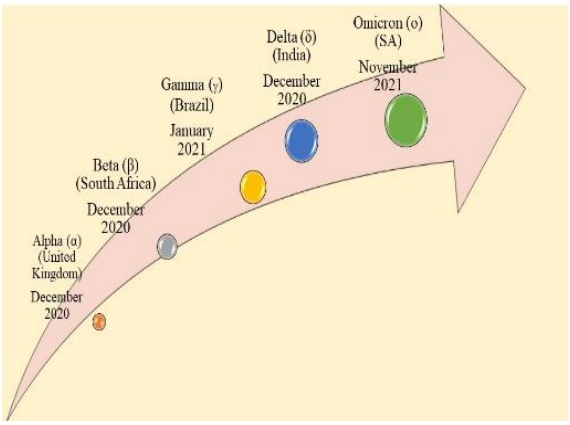

Fig 1. Different Variants of SARS-CoV-2 Recognized in Global Pandemic. [5]

The first incidence of COVID-19 was reported in India on January 30th, 2020. [3] So in a very short period, this disease spread worldwide. On 11th March 2020 (WHO) World health organization Announces SARS-CoV-2 i.e., COVID-19 as a Global Pandemic.

Worldwide mortality of more than 6,000,000 as of March 2022. This is the furthermost disastrous effect on the worldwide demographics. After the epoch of the pandemic influenza virus in the year of 1918, COVID-19 is the most consequential global health crisis. [4]

According to the studies, COVID-19 is infectious to humans as well as vertebrates. The gastrointestinal tract system and Respiratory tract system is the most important site of COVID19 Infection, along with this they also infect the Hepatic and nervous system. Different Variants of SARS-CoV-2 Recognized all over the Global Pandemic viz, Alpha. Beta, Gamma, Delta, and Omicron. [6]

IMMUNOMETABOLISM AND COVID-19

Immunometabolism refers to the changes in immune cells' intracellular metabolic pathways which are responsible for altering the function of immune cells [7]. Immune cell response is triggered by these changes. Immunometabolism aims to utilize the particular metabolic pathway of different immune cells for treating diseases. In concern to COVID-19 (SARS-CoV-2) infection, immunometabolism triggers the activation of the immune system after Covid-19 infection [8].

SARS-CoV-2 is a novel pathogen for humans. For effective activation of the adaptive immune response against the antigen for neutralizing it may expect to develop 2 to 3 weeks after coming in contact with the virus. Conversely, the mild diseased or asymptomatic infections of patients are probably controlled by the activation of innate immune response. Innate immune activation does not depend on T cells or antibody recognition [9].

Activation of innate immunity against the virus is supported by some hormonal components, which include soluble proteins for recognizing glycans present on the surface of the cell (Mannose Binding Lectin), complement system and system of coagulation-fibrinolysis, chemokines, interferons (IFN), Naturally occurring antibodies (IgM, IgA, and IgG). The innate immunity activation also possesses some cellular components, including Innate Lymphoid Cells (ILC), Natural Killer Cells (NK), and Gamma delta T cells. These cells generally control the viral infection spread by showing cytotoxic action on the target cells, adaptive response induction, and cytokine production [10].

After the entry of the virus into the host cell, viruses are recognized by Pattern Recognition Receptors (PRR) like TLR7, and TLR8 (in concern with ssRNA viruses) expressed by local innate immune response cells (alveolar macrophages) as well as epithelial cells. PRRs appoint adaptor proteins after ligand binding, and crucial downstream transcription factors are activated by those adaptor proteins, it includes NF-kB, Interferon Regulatory Factor (IRF), and AP-1, which results in the generation of Type-I and Type-III different chemokines and antiviral interferons. These chemokines are responsible to attract more cells of innate response cells (NK cells, polymorphonuclear leukocytes, dendritic cells (DC), monocytes). Those innate response cells also produce chemokines like IP-10, MIG, MCP-1, and viral antigens presented by dendritic cells are further recognized by it [11].

ENTRY MECHANISM OF CORONAVIRUS IN THE HUMAN CELL AND ITS LIFE CYCLE

In the downstream region of coronavirus, there is a presence of an ORF1 on a specific gene, it encodes a protein that is essential for viral replication [12]. The entry of the virus into a host cell is supported by the spike proteins present on the outer surface of the virus. The coronavirus entry mechanism mostly depends on cellular proteases including, cathepsins, HAT (Human Airway Trypsin) like Protease, and TMPRSS2 (Transmembrane protein serine-2) which establishes the penetration by conformational changes and splitting of spike proteins [13],[14].

S protein initially binds to ACE2 (angiotensin-converting enzyme) cellular receptor. Viral envelope and cell membrane fusion are facilitated by S proteins via an endosomal pathway. The virus releases its RNA into the host cell. The RNA further gets converted into pp1a and pp1ab (Viral replicase polyproteins). These polyproteins further get cleaved into viral proteinase products. The sub-genomic mRNA is produced by polymerase products through discontinuous transcription and it finally gets translated into equivalent viral proteins. In the Golgi body and ER, the genome RNA and viral proteins get assembled and further transported and release out of the cell via vesicles as given in figure 2.

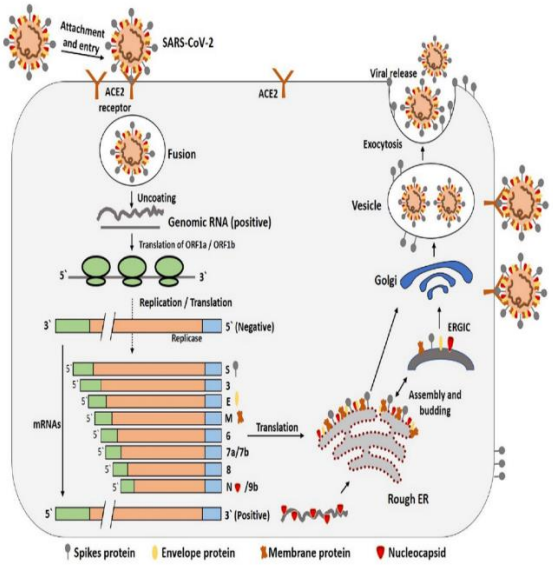

Fig 2. Life Cycle of Coronavirus Inside the Host Cell [15]

CLINICAL CHARACTERISTICS OF COVID-19 INFECTION

A wide range of disease symptoms can be observed in cases of confirmed and reported COVID-19 infection [16]. The common symptoms of COVID-19 infection include fever, shortness of breath, cough, chills, sore throat, diarrhea, muscle aches, unexplained loss of smell or taste, and headache [17]. These symptoms begin from mild to severe over 5-7 days. COVID-19 Symptoms appear from 2-14 days after viral exposure, due to which a quarantine period of 14 days is mandatory [16]. In some cases, infected individuals remain asymptomatic and approximately 80% of positive individuals get recovered without any medication [18]. But such an individual can act as a carrier to transmit disease [19].

COMORBIDITIES OF COVID-19

Comorbidities concerning COVID-19 refer to the presence of two or more medical consequences in an infected individual. Comorbidities can increase the rate of COVID-19 infection [16]. The elder population with chronic health disorders are like lung or cardiovascular disease, diabetes is the community under a high risk of getting infected and developing illness with high health risk after getting ill [19]. Peoples suffering from kidney, lung, liver disease, hypertension, cancer, diabetes, transplant recipients, patients taking steroids, and smokers are at very increased risk of infection [16]. As represented in Fig. 3, the surveillance reports based on the population COVID-19-Associated Hospitalization Surveillance Network has reported 1478 patients' data of COVID-19-positive and under hospitalization. The severity of infection based on comorbidities was analyzed [20]. The hospitalization rate of patients with characteristics of confirmed coronavirus infection was comparatively analyzed [20].

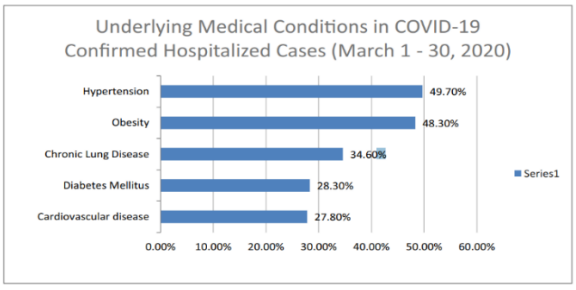

Fig 3. Effect of comorbidities on hospitalization rate of confirmed COVID-19 infected peoples [20].

VACCINE DISTRIBUTION WORLDWIDE

To overcome the situation of COVID-19 disease and its widespread all over the world, many vaccines were developed and are still under development by respected developing bodies with great efforts. The rapid development of the vaccine was the biggest achievement to tackle the pandemic but still, some questions arrived among the people regarding vaccine efficacy, its global demand, and production capacity [21].

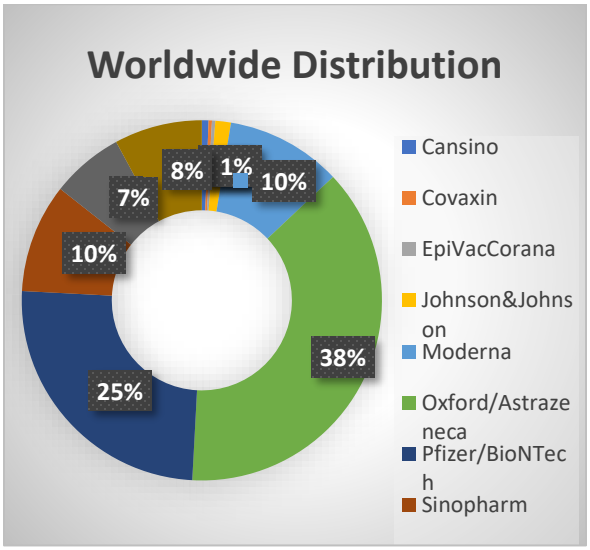

Fig 4. Vaccine Distribution Over Worldwide [22]

Since April 2021, 10 vaccines got approval for worldwide use which include, Covaxin, Johnson & Johnson, Sputnik V, Oxford/AstraZeneca, Sinopharm, EpiVacCorona, Pfizer/BioNTech, Moderna, and Sinovac. Around 193 countries started vaccination programs using these vaccines. Oxford/AstraZeneca vaccine is a highly used vaccine during vaccination programs. Pfizer/BioNTech vaccine is the second most preferred vaccine during the pandemic [21], [22]. Vaccine distribution all over the world is shown in fig 4.

EFFECT OF VACCINES ON IMMUNOMETABOLISM OF COVID-19 PATIENTS

The effect of the COVID-19 pandemic has great mortality and morbidity rate worldwide. Acquisition of immunity through vaccination or natural infection is required to control the pandemic situation as the COVID-19 viruses circulate continuously. Several mRNA vaccines have been developed which encode and stabilized the Spike protein of SARS-CoV-2 with 95% efficacy for preventing the severity of

symptomatic COVID-19 [23], [24]. Vaccines generate a humoral immune response, along with a generation of neutralizing antibodies for preventing disease [25], [26].

With antibody production, there is a requirement for long-life memory B cells and T cells generation for an effective immune response [27]. Memory B cells are specific for both the Spike receptor binding domain and spike proteins of SARS-CoV-2 [28], [29]. In the case of previously vaccinated persons, memory B cells and T cells get rapidly activated which helps to control the initial viral replication and limit the spread of the virus inside the host [30]-[32]. The memory B cells and T cells respond and prevent the viral infection from the first hours to days after viral exposure. Cellular immunity generated by vaccination can reduce or prevent the disease symptoms.

The emergence of novel variants of SARS-CoV-2 like Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) is also suppressed by evasion from immunity induced by vaccines (25–28). The memory B cells presence was found to be more in vaccinated persons as compared to the one who recovered from COVID-19 infection. The mRNA vaccine generates CD8+ T cells and CD4+ T cells in vaccinated individuals.

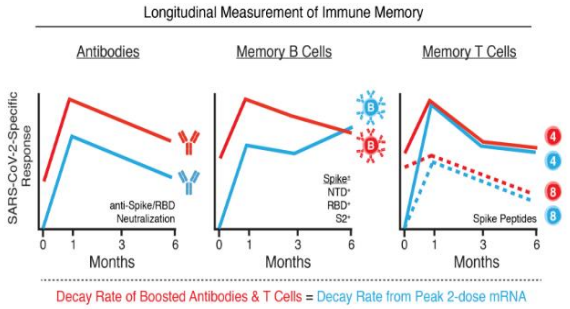

Figure 5. Immune memory measurement after Vaccination [33]

Without changing the decay rate or B cell and T cell memory of antibodies, the mRNA vaccines can recover increased antibody response of COVID-19 patients in a very short period. The evaluation of immunity induced by vaccination is represented in fig 5.

CONCLUSION

The given study represented the origin, dissemination, prevention, and recovery rate of COVID-19 virus infection. We also represented the life cycle and infection pattern of SARS-CoV-2. The Comorbidities and their effect on increasing the risk of COVID-19 virus infection are also discussed by which we come to know that the people having comorbidities like kidney, lung, liver disease, hypertension, cancer, diabetes, transplant recipients, patients taking steroids, smokers are at very increased risk of infection. Further, we studied the worldwide distribution of COVID-19 vaccines and the vaccine intake evaluation. The effect of the vaccine on immunometabolism of infected and recovered patients is also analyzed with the study of pre-and post-vaccinated patients. With antibody production, there is a requirement for long-life memory B cells and T cells generation for effective immune response, which can be obtained from vaccines as represented in our study.

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REFERENCE

[1] Agarwal, K. M., Mohapatra, S., Sharma, P., Sharma, S., Bhatia, D., & Mishra, A. (2020). Study and overview of the novel coronavirus disease (COVID-19). *Sensors international*, *1*, 100037.

[2] Chavez, S., Long, B., Koyfman, A., & Liang, S. Y. (2021). Coronavirus Disease (COVID-19): A primer for emergency physicians. *The American journal of emergency medicine*, *44*, 220-229.

[3] Patil, S. B. (2020). Indian Publications on SARS-CoV-2: A bibliometric study of WHO COVID-19 database. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(5), 1171-1178.

[4] Cascella, M., Rajnik, M., Aleem, A., Dulebohn, S. C., & Di Napoli, R. (2022). Features, evaluation, and treatment of coronavirus (COVID-19). *Statpearls [internet]*.

[5] Lei, J., Kusov, Y., & Hilgenfeld, R. (2018). Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. *Antiviral Research*, *149*, 58-74.

[6] Chen, Y., Liu, Q., & Guo, D. (2020). Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of medical virology*, *92*(4), 418-423.

[7] O'Neill, L. A., Kishton, R. J., & Rathmell, J. (2016). A guide to immunometabolism for immunologists. *Nature Reviews Immunology*, *16*(9), 553-565.

[8] Da Silveira, M. P., da Silva Fagundes, K. K., Bizuti, M. R., Starck, É., Rossi, R. C., & de Resende E Silva, D. T. (2021). Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. *Clinical and experimental medicine*, *21*(1), 15-28.

[9] Boechat, J. L., Chora, I., Morais, A., & Delgado, L. (2021). The immune response to SARS-CoV-2 and COVID-19 immunopathology–current perspectives. *Pulmonology*, *27*(5), 423-437.

[10] Batabyal, R., Freishtat, N., Hill, E., Rehman, M., Freishtat, R., & Koutroulis, I. (2021). Metabolic dysfunction and immunometabolism in COVID-19 pathophysiology and therapeutics. *International Journal of Obesity*, *45*(6), 1163-1169.

[11] García, L. F. (2020). Immune response, inflammation, and the clinical spectrum of COVID-19. *Frontiers in immunology*, *11*, 1441.

[12] Van Boheemen, S., De Graaf, M., Lauber, C., Bestebroer, T. M., Raj, V. S., Zaki, A. M., & Fouchier, R. A. (2012). Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. *MBio*, *3*(6), e00473-12.

[13] Glowacka, I., Bertram, S., Müller, M. A., Allen, P., Soilleux, E., Pfefferle, S., ... & Pöhlmann, S. (2011). Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *Journal of virology*, *85*(9), 4122-4134.

[14] Bertram, S., Glowacka, I., Müller, M. A., Lavender, H., Gnirss, K., Nehlmeier, I., ... & Pöhlmann, S. (2011). Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. *Journal of virology*, *85*(24), 13363-13372.

[15] Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique, R. (2020). COVID-19 infection: Emergence, transmission, and characteristics of human coronaviruses. *Journal of advanced research*, *24*, 91-98.

[16] Van Der Hoek, L., Pyrc, K., Jebbink, M. F., Vermeulen-Oost, W., Berkhout, R. J., Wolthers, K. C., & Berkhout, B. (2004). Identification of a new human coronavirus. *Nature medicine*, *10*(4), 368-373.

[17] Rahman, A., & Sarkar, A. (2019). Risk factors for fatal middle east respiratory syndrome coronavirus infections in Saudi Arabia: analysis of the WHO Line List, 2013–2018. *American journal of public health*, *109*(9), 1288-1293.

[18] Memish, Z. A., Zumla, A. I., Al-Hakeem, R. F., Al-Rabeeah, A. A., & Stephens, G. M. (2013). Family cluster of Middle East respiratory syndrome coronavirus infections. *New England Journal of Medicine*, *368*(26), 2487-2494.

[19] Kan, B., Wang, M., Jing, H., Xu, H., Jiang, X., Yan, M., .& Xu, J. (2005). Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus-like virus in pal

[20] Peiris, J. S., Guan, Y., & Yuen, K. (2004). Severe acute respiratory syndrome. *Nature medicine*, *10*(12), S88-S97.

[21] Dhama, K., Sharun, K., Tiwari, R., Dadar, M., Malik, Y. S., Singh, K. P., & Chaicumpa, W. (2020). COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Human vaccines & immunotherapeutics*, *16*(6), 1232-1238.

[22] Fukutani, K. F., Barreto, M. L., Andrade, B. B., & Queiroz, A. T. (2021). Correlation between SARS-Cov-2 vaccination, COVID-19 incidence, and mortality: Tracking the effect of vaccination on population protection in real-time. *Frontiers in genetics*, *12*, 679485.

[23] Thomas, S. J., Moreira Jr, E. D., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., ... & Jansen, K. U. (2021). Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *New England Journal of Medicine*, *385*(19), 1761-1773.

[24] Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., & Zaks, T. (2020). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England journal of medicine*.

[25] Khoury, D. S., Cromer, D., Reynaldi, A., Schlub, T. E., Wheatley, A. K., Juno, J. A., ... & Davenport, M. P. (2021). Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature medicine*, *27*(7), 1205-1211.

[26] Gilbert, P. B., Montefiori, D. C., McDermott, A. B., Fong, Y., Benkeser, D., Deng, W., & United

States Government (USG)/CoVPN Biostatistics Team §. (2022). Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*, *375*(6576), 43-50.

[27] Turner, J. S., O'Halloran, J. A., Kalaidina, E., Kim, W., Schmitz, A. J., Zhou, J. Q., & Ellebedy, A. H. (2021). SARS-CoV-2 mRNA vaccines induce persistent human germinal center responses. *Nature*, *596*(7870), 109-113.

[28] Goel, R. R., Apostolidis, S. A., Painter, M. M., Mathew, D., Pattekar, A., Kuthuru, O., & Wherry, E. J. (2021). Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals after mRNA vaccination. *Science Immunology*, *6*(58), eabi6950.

[29] Mazzoni, A., Di Lauria, N., Maggi, L., Salvati, L., Vanni, A., Capone, M., & Annunziato, F. (2021). First-dose mRNA vaccination is sufficient to reactivate immunological memory to SARS-CoV-2 in subjects who have recovered from COVID-19. *The Journal of clinical investigation*, *131*(12).

[30] Cromer, D., Juno, J. A., Khoury, D., Reynaldi, A., Wheatley, A. K., Kent, S. J., & Davenport, M. P. (2021). Prospects for durable immune control of SARS-CoV-2 and prevention of reinfection. *Nature Reviews Immunology*, *21*(6), 395-404.

[31] Akkaya, M., Kwak, K., & Pierce, S. K. (2020). B cell memory: building two walls of protection against pathogens. *Nature Reviews Immunology*, *20*(4), 229-238.

[32] Farber, D. L., Yudanin, N. A., & Restifo, N. P. (2014). Human memory T cells: generation, compartmentalization, and homeostasis. *Nature Reviews Immunology*, *14*(1), 24-35.

[33] Goel, R. R., Painter, M. M., Apostolidis, S. A., Mathew, D., Meng, W., Rosenfeld, A. M., ... & Wherry, E. J. (2021). mRNA vaccination induces durable immune memory to SARS-CoV-2 with continued evolution to variants of concern. *Biorxiv*.