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Immunology in COVID-19

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ABSTRACT

So far, no effective vaccines or medicines have been licensed to prevent or treat the virus's rapid and global spread, urgent research is required to find preventative and therapeutic medicines. Treatments that target the immunopathology of SARS-CoV-2 infection have been a key focus in this respect.

While a fast and well-coordinated immune response is the first line of defense against viral infection, an overly inflammatory innate response and a weakened adaptive host immunological response can cause tissue damage both at the site of virus entry and at the systemic level. Several investigations have identified significant alterations in the innate and adaptive immune systems in COVID-infected people.

The enormous production of cytokines and chemokines, known as a "cytokine storm," plainly shows an uncontrolled dysregulation of the host immunological response. Although the idea of preventing cytokine storms is appealing, one important drawback is the lack of knowledge about the immunological signaling pathways triggered by SARS-CoV-2 infection. The discovery of altered signaling pathways during viral infections may aid in the deciphering of the most important molecular cascades involved in biological processes driving viral infections, as well as the identification of key molecular actors that might be targeted.

Given the immune system's central involvement in COVID-19, a better understanding of the mechanism behind immunological dysregulation might lead to better therapeutic care of severe instances and the prevention of the disease's progression from moderate to severe. COVID-19 and supportive therapy remain the current standard of care.

Keywords: COVID-19, SARS-CoV-2 infection, immunology, coronavirus illness 2019

INTRODUCTION

Coronavirus illness 2019 (COVID-19), also known as coronavirus or COVID, is a contagious disease caused by a virus that causes severe acute respiratory syndrome (SARS-CoV-2). The first known case was found in Wuhan, China, in December of this year. The disease has since spread throughout the world, resulting in a pandemic (Hengbo *et al.*, 2020).

COVID-19 symptoms include fever, cough, headache, tiredness, breathing problems, and loss of smell and taste (Cascella et al., 2022). Symptoms may appear one to fourteen days after being exposed to the virus. At least one-third of those who are afflicted do not exhibit any signs or symptoms. The majority of people who develop noticeable symptoms enough to be classified as patients have mild to moderate symptoms (up to mild pneumonia), while 14% have severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% have critical symptoms (respiratory failure, shock, or multiorgan dysfunction) (Stephen et al., 2020). Severe symptoms are more likely to appear in the elderly. Some people keep going. Some persons experience a range of symptoms months after they have recovered (long COVID), and organ damage has been documented. Long-term studies are

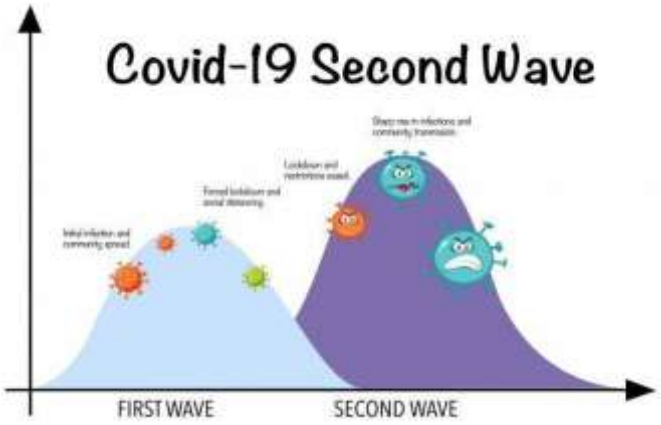
being carried out to learn more about the disease's long-term effects (Arevalos et al., 2021).

COVID-19 develops when people are exposed to virus-containing respiratory droplets and airborne particles exhaled by an infected person (Mahesh et al., 2020). Infected people, including those who don't show symptoms, can spread the virus to others up to two days before they show symptoms. People can be infectious for up to ten days after symptoms develop, and they can be infectious for up to twenty days in severe cases (Daniel et al., 2020).

Coronavirus cases have been reported in 220 countries throughout the world, with the United States reporting the largest number of cases and fatalities. Up to May 25th, 2021, India is ranked second on the list, with a population of 2.7 crores and 3.1 lakh fatalities (Khan et al., 2020, WHO, 2020).

The Covid epidemic has struck India twice so far. During the initial peak in September 2019, the number of Covid infections reached an all-time high of 97,000 infections per day. Despite this, the country escaped largely unharmed, giving the mistaken impression that the worst had passed (Pranab *et al.*, 2020).

When the second wave hit in April 2020, India was woefully unprepared to deal with the avalanche of cases. In identical wave-like patterns, the virus has hit numerous countries throughout the world (Sujita *et al.*, 2021).



PATHOPHYSIOLOGY

Coronaviruses are 30 kb Positive-sense single-stranded RNA viruses with a single-stranded RNA genome were enclosed. They have the ability to infect a wide variety of hosts. They are primarily classified into four genera based on their genetic structure, and coronaviruses can only infect animals (Mahendra et al., 2020).

The five stages of the virus's life cycle with the host are attachment, infiltration, biosynthesis, maturity, and release. After binding to host receptors (attachment), viruses enter host cells via endocytosis or membrane fusion (penetration). Once the viral contents are released into the host cells, viral RNA enters the nucleus for replication. To produce viral proteins, viral mRNA is utilized (biosynthesis). Then, upon maturity, more virus particles are produced and discharged. Spike (S), membrane (M), envelope (E), and nucleocapsid (N) are the four structural proteins of Coronaviruses (N). Spike is a transmembrane trimetric glycoprotein that protrudes from the viral surface and is responsible for coronavirus variety as well as host tropism. The S1 subunit is responsible for attaching to the host cell receptor, whereas the S2 subunit is important for fusing the viral and cellular membranes. SARS-CoV has been found to have a functional receptor, angiotensin-converting enzyme 2 (ACE2). The spike for SARS-CoV-2 is linked to ACE2 according to structural and functional analyses. The

lung, heart, ileum, kidney, and bladder all have elevated levels of ACE2. On lung epithelial cells, ACE2 was significantly expressed. Following SARS-attachment CoV-2's to the host protein, the spike protein is cleaved by proteases. The coronavirus spike is unique among viruses in that it may be cleaved and activated by a variety of proteases. The presence of a furin cleavage site ("RPPA" sequence) at the S1/S2 site distinguishes SARS-CoV-2 from other coronaviruses. Furin's widespread expression renders this virus extremely pathogenic (Philip *et al.,* 2021; Yuki *et al.,* 2020).

The virus penetrates the pulmonary alveolar epithelial cells after membrane fusion and releases the viral contents within. The virus now replicates inside the host cell, using the pre-existing single-strand positive RNA to produce a negative-strand RNA through RNA polymerase activity (transcription). This freshly generated negative-strand RNA is used to generate new positive RNA strands, which are subsequently used to synthesize new proteins in the cell cytoplasm (translation). The viral N protein attaches to the new genomic RNA, while the M protein helps the virus integrate into the cellular endoplasmic reticulum (Muhammad *et al.,* 2020).

These freshly produced Nucleocapsids are subsequently contained in the ER membrane and transferred to the lumen, where they are delivered to the cell membrane through Golgi vesicles, and finally to the extracellular space by exocytosis. The new virus particles are now available to infect neighbouring epithelial cells and provide fresh infectious material for community transmission via respiratory droplets (Boopathia *et al.,* 2020).

IMMUNOLOGY

Asymptomatic Phase

SARS-CoV-2 binds to nasal epithelial cells after entering the upper respiratory tract via respiratory aerosols. The ACE-2 receptor, which is abundantly expressed in adult nasal epithelial cells, is the primary host receptor for viral entry into cells. Locally, the virus replicates and multiplies, infecting ciliated cells in the conducting airways. This stage lasts a few days and results in a minimal immune response. The patients are exceedingly contagious, despite having a low viral load at this time, and the virus can be diagnosed by nasal swab testing (Daniel et al., 2020).

Invasion and Infection of Upper Respiratory Tract

The virus migrates from the nasal epithelium to the upper respiratory tract through the conducting airways at this stage. The disease presents as fever, lethargy, and dry cough due to the involvement of the upper airways. During this phase, the release of C-X-C motif chemokine ligand 10 triggers a stronger immunological response.

The virus-infected cells produced CXCL-10 and interferons (IFN- and IFN-). The majority of patients do not advance past this stage because the built-up immune response is adequate to prevent infection from spreading (Subbarao and Siddhartha, 2020.).

Progression To Acute Respiratory Distress Syndrome (ARDS)

Approximately one-fifth of all infected people reach this stage of the illness and experience severe symptoms. The virus infiltrates and penetrates type 2 alveolar epithelial cells via the host receptor ACE-2, where it begins replication to generate new viral Nucleocapsids. Among the cytokines and inflammatory markers released by virus-infected pneumocytes are interleukins (IL-1, IL-6, IL-8, IL-120, and IL-12), tumour necrosis factor (TNF-), IFN-, and IFN-, CXCL-10, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1 (MIP-1) (Aslan et al., 2021). This cytokine storm attracts neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells, which are eventually trapped in lung tissue. These cells not only fight the virus, but they also deal with the resulting inflammation and lung damage. The host cell dies, releasing more virus

particles that infect neighbouring type 2 alveolar epithelial cells. Both type 1 and type 2 pneumocytes are lost as a result of continuous damage caused by sequestered inflammatory cells and virus replication. As a result of widespread alveolar damage, acute respiratory distress syndrome develops (Chowdhury et al., 2020).

IMMUNITY

Humans' immune response to the CoV-2 virus is a mix of cell-mediated immunity and antibody generation, as it is with most other infections. Since SARS-CoV-2 has only been in the human population since December 2019, it's unclear if those who recover from the sickness will develop long-term immunity. The presence of neutralising antibodies in the blood is closely linked to infection protection, although neutralising antibody levels drop with time. Two months after infection, those with asymptomatic or moderate illness had undetectable levels of neutralising antibodies (Rebecca and Karl, 2020). Another study found that one to four months following the beginning of symptoms, the amount of neutralising antibodies dropped fourfold. However, the absence of antibodies in the blood does not rule out the possibility that antibodies may be generated quickly if SARS-CoV-2 is reintroduced. Memory B lymphocytes specific for SARS-CoV-2 spike and nucleocapsid proteins remain for at least six months after symptoms emerge (Jennifer et al., 2021).

Despite this, 15 cases of SARS-CoV-2 reinfection have been documented, with the CDC needing the identification of a distinct variation from the second infection. Many more people are likely to have been infected with the virus again. If the virus is re-infected frequently, herd immunity will not be effective. Other coronaviruses that are circulating in humans can reinfect people after about a year (Vitale et al., 2021). Nonetheless, on March 3, 2021, scientists revealed that a far more contagious COVID-19 variation, Lineage P.1, had been discovered in Japan, Brazil, and many locations in the United States. After recovering from a prior COVID-19 infection, states may be linked to COVID-19 illness reinfection (William et al., 2021).

Amazingly, the immune response's involvement in the infection is required for pathogen clearance, cellular homeostasis, tissue healing, and memory cell formation. Over time, research into that complex system and how it interacts with infections has become more prominent. This is critical because it allows us to gain a better understanding of the pathogen, particularly how it acts on this system, and how we can use that knowledge to develop effective methods to control and eradicate a disease (Chowdhury et al., 2020).

In reality, a collective study is impossible since each individual will have a response to this infection, which might adapt. What is the cause for the high level of lymphocyte activation in asymptomatic people? They can facilitate the activation of numerous immune system components, as well as the formation of memory cells and the balance of the immune response because they are important cells in a more effective response. The key question is whether other cell types (for example, neutrophils and macrophages) or lymphocyte sequestration maintain the response in severe patients. Because the virus multiplies, the immune reaction gets stronger and more severe, resulting in pathology such as cell infiltration and fibrosis, among other things, which inhibits the organ from working properly, resulting in respiratory system debilitation. We can nevertheless report that anti-inflammatory mediators are produced in these individuals as a method to maintain the dynamic balance between anti- and pro-inflammatory responses and that the inflammatory response is attenuated, which facilitates viral survival (Zeyu and John, 2020.).

On the other hand, individuals with the mild and asymptomatic form of the disease's immune system are likely to effectively "control or eliminate" the virus, resulting in a continuous flow of the inflammatory response (inflammation to the resolution of

the response) and no development of severe pathologies associated with exacerbated inflammation. As a result, the inflammatory response during infection appears to be critical in determining the disease's progress.

Thus, not only the activation factor but also how the response is regulated, maintaining the balance of anti- and pro-inflammatory components, is a crucially important element in the immune response. When this balance is achieved, the reaction will be more efficient, resulting in less harm to the host (Linlin *et al.*, 2018; Luis 2020).

VACCINE

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is causing the coronavirus disease 2019 (COVID-19) pandemic, which is humanity's most catastrophic threat in a century. Normally before a pandemic is widely believed to be difficult to achieve unless a safe and efficient vaccine is discovered and a global vaccination programme is successfully carried out (Kaur and Vandana, 2020).

The magnitude of the Coronavirus Disease 2019 (COVID-19) pandemic, which is characterised by acute respiratory syndrome (sars) might be increased if contemporary medical care and vaccinations are not available (SARS)

Fever is one of the signs. These signals are typical and indicate that the body is strengthening its defenses.

The coronavirus 2 (SARS-CoV-2) pandemic might be on par with the 1894 plague (12 million fatalities) and 1918 A(H_1N_1) influenza pandemics (50 million deaths) (Jun, 2020).

Vaccinations provide different sorts of protection in different ways. All immunizations, on the other hand, leave the body with a supply of "memory" T- and B-lymphocytes that will remember how to fight the virus in the future.

T-lymphocytes and B-lymphocytes are produced by the body a few weeks after immunization. As a result, a person could become infected with the COVID-19 virus shortly before or after vaccination, and become unwell as a result of the vaccine not having enough time to act (Zeyu and John, 2020).

COVID 19 VACCINATION IN INDIA CURRENT STRATEGY

INTRODUCTION

Free COVID-19 vaccinations began on January 16, 2021, in India, and the government is urging all of its citizens to get vaccinated as part of what is expected to be the world's largest immunization campaign. India, which has a population of 1380 million people (as of 2020), plans to provide the vaccine to every one of its citizens who request it. In India, four of the eight COVID-19 vaccines currently in clinical studies were developed. The country's pharmaceuticals board has approved Covishield (the Oxford-AstraZeneca vaccine) and Covaxin, a domestic vaccine developed by Bharat Biotech, for limited emergency use in India. India's COVID-19 vaccine manufacturers have stated that they can meet the country's future requests. The Indian government has moved quickly to increase the country's vaccine manufacturing capacity, as well as to develop an effective digital system to address and track all aspects of vaccine delivery (Velayudhan *et al.*, 2020).

India, has a robust vaccine development plan, that aims to manufacture the COVID-19 vaccine in-house and disseminate it to countries that cannot pay to obtain costly immunizations from the West. Even though some specifics are still unknown, clinical observation trials of many vaccines in India claim to support their suitability for the case of emergency permission. The main emphasis for these vaccinations is on quality control, production quality, and cost management to make them affordable to even the world's poorest countries (Charlene et al., 2020).

MATERIAL AND METHOD

COVAXIN

Covaxin was developed by Bharat Biotech International Ltd of Hyderabad in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology is the study of viruses (NIV). Covaxin is an inactivated vaccine that was developed on a well-proven platform of dead viruses (Kamala, 2021).
This vaccine is developed with Whole-Virion Inactivated Vero cell derived technology. They contain inactivated viruses, which cannot infect a person but still can teach the immune system to prepare a defense mechanism against the active virus (Chandrakant, 2014).

COVISHIELD
The Oxford-AstraZeneca company created Covishield, which is produced by the Serum Institute of India (SII).
The viral vector platform, which is a completely distinct technology, was used to create Covishield.
ChAdOx1 is an Adenovirus in chimps that have been engineered to introduce the COVID-19 jolt protein into one of the living cells Although this cold virus is unable to infect the recipient and prepare the immunity to advance. a defense mechanism towards similar viruses (Correspondence, 2021).

DOSE
In terms of dosage, there is no difference between the two vaccines. Both of them are on a two-dose schedule that is given 28 days apart (Fernando et al., 2020).

STORAGE GUIDELINE
Covishield and Covaxin can both be kept at 2-8 degrees Celsius, which is the temperature of a standard refrigerator. Because most vaccinations in India are stored at the same temperature range (Michelle, 2021).

SIDE EFFECT
You may have soreness at the injection site after receiving the immunisation. Some people also have adverse symptoms including headaches, joint pain, and a feverish feeling. These adverse effects do not last long and usually disappear after a day or two (Cristina et al., 2021).

MODE OF ADMINISTRATION
Intramuscular vaccinations, such as Covaxin and Covishield, are available.

AGE OF BENEFICIARY
Covishield is only for persons over the age of 18, whilst Covaxin is for children over the age of 12. The vaccine's suitability for youngsters and pregnant women, however, is unknown (Walter et al., 2021)

EXCLUSION CRITERIA
- Infected people, such as those with HIV and hepatitis
- Pregnancy
- Within three days of each dose, you must be free of an upper respiratory infection or gastroenteritis.
- Cardiovascular illness that is severe and/or uncontrolled
- Among the illnesses that can affect you are nosocomial infection, gastrointestinal disorders, liver problems, kidney problems, hormonal disorders, and neurological disorders are all possibilities.
- Individuals who screened positive for SARS-CoV-2 nucleotides and/or serology (WHO, 2021).

METHODS
Blood samples were taken on the day before immunisation, as well as seven, fourteen, twenty-eight, and fifty-six days later. The humoral immune response in Indian health care workers (HCW) after receiving the first dose of two vaccinations, ChAdOx1-nCOV (CovishieldTM) and BBV-152 (CovaxinTM) (Awadhesh *et al.,* 2021).
This operational pan-India, cross-sectional Coronavirus Vaccine-induced Antibody Titre study (COVAT) investigation is being carried out among HCW with or without a history of SARS-CoV-2 infection. Anti-spike binding antibodies to SARS-CoV-2

are being measured at four time - points, spanning from 21 days to 6 months following the first treatment. The main purpose is to examine the antibody response to both vaccines after each dose and observe how it is associated with age, gender, BMI, and comorbidity. The initial anti-spike antibody response data after the first dose is shown below (Sabina *et al*., 2021).

RESULTS

456 HCW (325 Male, 227 Female) and 96 HCW (325 Male, 227 Female) received their initial doses of Covishield and Covaxin, respectively. After the first dose, 79.3 % of the participants were seropositive. Covishield patients showed a significantly higher reaction rate and average (IQR) anti-spike antibody increase than Covaxin recipients (86.8percent) of the respondents vs. 43.8%) and 61.5 vs. 6 AU/ml, respectively; both p0.001). In 172 patients, the difference remained after propensity-matched (age, sex, and BMI) analysis. There was no difference in age, gender, or BMI. Hypertension history was associated with a reduced responder rate (65.7 vs. 82.3 percent, p=0.001). In comparison to the Covaxin arm, Covishield recipients had greater adverse events (46.7 vs. In an investigation of numerous logistic regressions, the occurrence of coexisting conditions, previous the illness was SARS-CoV-2, and the vaccines used were all Seropositivity after the first dosage is predicted by independent predictors.

CONCLUSION

Although both vaccines elicited an immune reaction, Covishield users had a significantly higher level of protection greater After the first dose, anti-spike antibody seropositivity rates were higher in Covaxin patients than in non-Covaxin recipients. The current COVAT trial will provide more information about the immune response to the second of two vaccine doses.

HIGHLIGHTS

1. Two SARS-CoV-2 vaccinations elicited humoral antibody responses, CovishieldTM and CovaxinTM, in Indian healthcare professionals was investigated in this study.
2. Anti-spike antibody seropositivity was seen in both vaccinations 21 days or longer after the first dosage.
3. In propensity-matched cohorts, responder rates were greater in Covishield recipients than in Covaxin recipients.
4. Previous After the first dosage, SARS-CoV-2 infection, comorbidities, and vaccination type were all independent predictors of antibody response.

PREVENTION

Getting the vaccine, staying at home, wearing masks in the general populace, avoiding crowded places, maintaining a safe spacing from others, ventilating indoor spaces, trying to manage possible exposure durations, handwashing frequently and for at least 15 to 20 seconds, developing positive respiratory hygiene, and avoiding trying to touch the eyes, nose, or mouth are all methods of preventing of infection (Melika *et al.*, 2020).

CONCLUSION

COVID-19 is a real pandemic that is infecting individuals all over the world. Current management consists of reducing the viral spread and providing supportive care for sick individuals in the absence of basic therapeutic treatments. The development of tailored treatments is critical. Understanding the differences between the reactions of children and adults to this virus may aid in the development of immune-based therapies.

Declaration by Authors

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