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DELTA VARIANT: A WORLDWIDE PUBLIC HEALTH HAZARD AND ITS MANAGEMENT

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ABSTRACT: The whole world facing unpredictable problems with different variants of COVID-19; B.1.617.2 is the newest form of SARS- CoV-2.It is evolving through mutations to consistently being a risk to public health. Recently, the Delta variant has been declared as the variant of concern by the World Health Organization (WHO). Delta Plus has been presented to provide a relevant foundation for future research works. Mutations are causing SARS-CoV-2 to alter its genetic structure to improve its potential to elude the immune system, making vaccine build out against the virus more difficult. Multiple SARS-CoV-2 variants have been found up to this point; based on their impact on public health some are considered variants of concern (VOCs) and some are considered variants of interests. VOCs are linked to superior transmissibility, a decline in neutralization by natural or vaccine-induced antibodies, evading capability of detection, and a reduction in the efficacy of vaccines or therapeutics. In this article, a SARS-CoV-2 subtype, known as Delta, has been revised to provide the current state of the art and an appropriate foundation for future research works. The evolution, pathogenesis, current trends of transmission, associated symptoms, suggested prevention and treatments, and vaccine efficacy of the Delta variant are reviewed and discussed.

Key Words: Delta variant, COVID-19, Omicron, Remdesivir

I.INTRODUCTION:

The Coronavirus disease 2019 (COVID-19) pandemic has been surging for almost two years. More than 260 million confirmed cases have been reported according to the statistics of the World Health Organization (WHO), including five million deaths. WHO declared Delta as a variant of interest on April 4, 2021, then it was declared as a variant of concern on May 11, 2021 [2]. As of October 21, 2021, the United States has submitted the highest number of Delta Variant sequences to GISAID, the number being 642,725. The United Kingdom has submitted 624,244 cases while Germany has 82,453 and Denmark has 59,196 sequences submitted. Since the beginning of the outbreak, the virus has been going through mutations to change itself and making the task of the health professionals and researchers a lot harder. Almost ten principal variants of SARS-CoV-2 have been reported so far. Among them, Alpha, Beta, Gamma, and Delta have been termed Variants of Concern (VOC) based on their significance to global public health. Delta variant was first reported in India and recently it has emerged as the dominant variant across the world; almost 100% of the current cases in most countries are consequences of this variant. Delta variant is more infective as well as it is causing higher transmissibility compared to all other variants. Delta causes a significant number of breakthrough infections in vaccinated individuals. A sublineage of Delta established as "Delta Plus" has been reported to be a health concern by Public Health England. They claimed that this muted variant was detected in six genomes from India till June 7, 2021. Most of the vaccines against COVID use the spike protein to trigger the body's immune system, a mutation in the spike protein can change the way the vaccines work and deteriorate the protection against the coronavirus [6]. More recently, another "plus" variant of Delta (AY.4.2) is triggering serious concern across UK and USA. UK reported that this variant spiked to 11% of the current total COVID cases while it spread to at least 8 states in the USA. Based on what is known so far, Delta Plus is considered highly infectious. It is gradually spreading throughout

the world making it a headache for researchers and health professionals. COVID-19 has been a nightmare for billions of people all over the world impacting their lives with unprecedented losses be it economic, physical, or mental. As of October 20, 2021, there have been about 244 million cases and 4.95 million deaths due to COVID; the United States, India, Brazil, the United Kingdom, and Russia are leading the list for most COVID cases [1]. New cases on October 21, 2021, show that the UK, Russia, Turkey, and Romania are following the USA, a comparison of total and new cases categorized by countries. Although there have been vaccines that are very effective to protect against coronavirus, the number of cases and deaths is still rising. One critical reason behind this increase is the mutation capability of the virus. SARS-CoV-2 has been going through several genomic alterations and is strongly spreading all over the world despite the prevention and vaccination efforts. World Health Organization (WHO) categorizes these variants depending on their transmissibility, virulence, and overall impact on health to prioritize worldwide surveillance and investigation, and eventually to report on the enduring retort to the deadly disease. Another concerning issue is that people infected with the Delta variant, whether they are vaccinated or not, can transmit the virus to others. It is also spreading more easily among children. [5]. According to the Centers for Disease Control and Prevention (CDC), Delta represented barely 0.1% of cases in the USA by early April.

I.THE DELTA VARIANT: STRUCTURE AND MUTATIONS

In India, samples of variant Delta (B.1.617.2) were located for the first time in October 2020. There are 13 mutations in the B.1.617.2 genome that cause changes in the amino-acid sequences of the encoded proteins. Four specific mutations located in the virus's spike protein code are very concerning, they are T478K, D614G, L452R, and P681R. Delta variant has gone through several significant mutations in the spike protein and spread into a few subtypes, which are classified as Delta Plus. The subtypes AY.1, AY.2, AY.3, and AY.4 are referred to as Delta Plus. They are structurally very analogous to the original Delta variant, but it contains a few changes. Delta Plus has a K417N mutation in the spike protein which is a lysine-to-asparagine substitution at position 417 [9]. The spike protein of this variant, according to Becerra et al. has the same LCRs as the SARS-CoV-2 Delta spike protein [10]. According to [11], The Delta and Delta Plus variants have distinct mutation patterns, and the Delta Plus is not just the Delta variant with On the Delta Plus Variant of SARS-CoV-2 Selia Chowdhury and Mehedi Hasan Bappy ABSTRACT The unprecedented consequences brought by the COVID pandemic are still going on, the virus hasn't been tamed yet. It is evolving through mutations to consistently being a risk to public health. Recently, the Delta variant has been declared as the variant of concern by the World Health Organization (WHO). In this article, Delta Plus has been presented to provide a relevant foundation for future research works. The evolution, pathogenesis, associated symptoms, suggested prevention and treatments, vaccine efficacy, and current trends of transmission of the Delta Plus variant of SARS-CoV-2 are reviewed and discussed. They reported that, in comparison to the Delta variant, the Delta Plus contained a higher percentage of high-prevalence mutations (20%). Three specific mutations (A222V, G142D, and T95I) in spike protein occurred at a higher fraction in the Delta Plus than in the Delta. Another three mutations in the spike protein are unique to the Delta Plus variant (V70F, K417N, and W258L). Additionally, they identified a novel alteration in ORF1a (A1146T); this was distinctively present in the Delta Plus variant with approximately 58% prevalence. They showed that five mutations (T95I, A222V, G142D, R158G, and K417N) are markedly more frequent in the Delta Plus than in the Delta variant. The genome can modify the pathogenic potential of a virus. When an animal or person is infected, mutations in the genetic coding of the virus develop spontaneously over time. It's critical to keep an eye on circulating viruses for significant mutations in key areas of the genome. Many mutations, on the other hand, have little effect on the virus's capacity to propagate or cause disease because they do not change the main proteins involved in infection; eventually, these variations are outcompeted by variants with more advantageous changes. Spike (S), envelope (E), membrane (M), and nucleocapsid (N) are four structural proteins, and nine potential accessory factors are located among them. The spike protein section contains genetic instructions for constructing the spike protein granting SARS-CoV-2 to adhere to human cells during infection. This portion of the genome is crucial for tracking mutations [8]. The variant Delta is alternatively recognized as B.1.617.2, comprises constructively selected mutations in the spike protein, the mutations include T478K, P681R, L452R, as well as the D614G. These mutations may be regarded as Delta variant hallmark characteristics. The spike protein forms trimers, which then form large structures termed spikes or peplomers that protrude from the virion's surface. These spikes must locate receptors in human cells to attach to; investigations have revealed that these spikes bind to ACE-2 receptors. The infection spreads by reproducing the virus's genetic code once these spike proteins have unlocked the cells. There are 13 mutations in the B.1.617.2 genome that cause changes in the amino acid sequences of the encoded proteins. The

spike protein substitutions corresponding to the Delta variant are T478K, T19R, P681R, D614G, T95I, D950N, G142D, R158G, L452R, F157-, E156-, (A222V*), (V70F*), (K417N*), and (W258L*), according to CDC. Particularly concerning are four of them inside the spike protein code of the virus.

1. L452R: The leucine-to-arginine change at position 452 gives higher attraction of the spike protein for the ACE2 receptor as well as reduced immune system identification capacity. These changes are not unique to the variation when considered separately; rather, their simultaneous presence is.
2. T478K: A threonine-to-lysine substitution occurs at position 478.
3. D614G: The aspartic acid-to-glycine alteration at position 614 is communal to other highly transmissible variants such as Alpha, Beta, and Gamma.
4. P681R: The proline-to-arginine substitution at position 681 may increase the variant's cell-level infectivity by enabling cleavage of the S precursor protein to the working S1/S2 configuration.

Major changes in the Delta variant discussed above make it simpler for the virus's spikes to bind to ACE-2 receptors. This means it can infect and multiply more quickly, as well as more effectively escape the body's natural disease-fighting defenses. According to the WHO, the spike protein changes make the Delta variation the fittest version yet. Furthermore, the presence of two medically significant point mutations, P681R and D950N, in these LCRs, along with their remarkable conservation, implies that they might be a characteristic linked to the fast spread of the highly infectious Delta lineage. The Delta variant has gone through several major mutations in the spike protein and spread into a few subtypes, which are classified as Delta Plus. AY.1, AY.2, and AY.3 are referred to as Delta Plus and they are structurally alike to the primary Delta variant, but it contains a few changes [14]. Delta along with Delta Plus variants exhibit distinct mutation patterns, and not just a K417N addition to the Delta makes the Delta Plus. The Delta Plus variation has three additional mutations in the spike protein: W258L, V70F, and K417N. They further recognized a novel mutation in ORF1a (A1146T), exclusively present with 58% prevalence in the Delta Plus variant. They also reported that five critical mutations are substantially more common in Delta Plus than in Delta: A222V, T95I, G142D, K417N, and R158G. There is not much difference in the clinical manifestations of people infected with the delta variant compared to the original COVID strain.

Comparison between Delta variant and omicron: Since Omicron was detected in

South Africa in late November, the SARS-CoV-2 variant has spread to more than 165 countries and is now the dominant strain.

Omicron has more mutations than other strains: 72 in total, the most concerning of which makes the virus more transmissible and better able to evade the immune system and vaccines.

So how does Omicron differ from Delta in infectiousness, symptoms, severity, and vaccine protection.

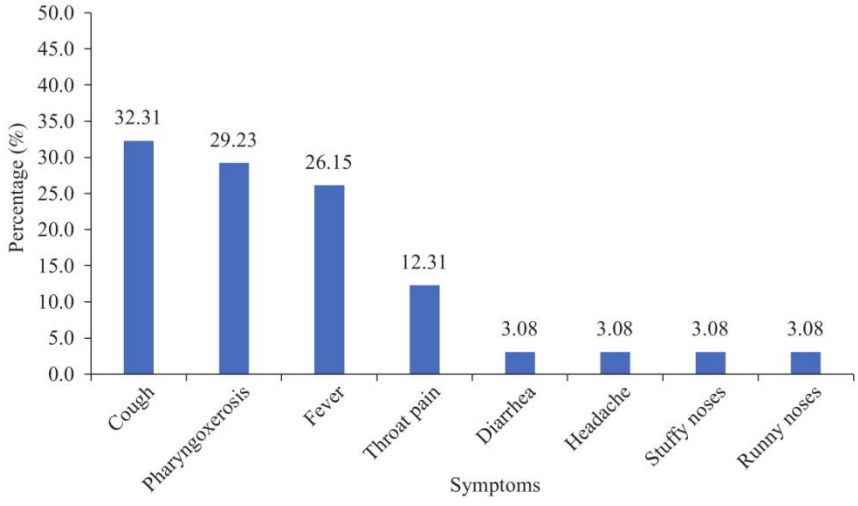

Fig. Symptoms among 65 Covid-19 cases infected with Omicron variant

TABLE 1. Comparation between 65 imported cases infected with Omicron variant and 78 imported cases infected with Delta variant.

Variable	Cases infected with Omicron variant (%) (n=65)	Cases infected with Delta variant (%) (n=78)	Chi-square test	*P* value
Gender				
Male	41 (63.08)	62 (79.49)	4.74	0.029*
Female	24 (36.92)	16 (20.51)		
Age (years)				
1–10	4 (6.15)	2 (2.56)		
11–20	2 (3.08)	0 (0.00)		
21–30	23 (35.38)	12 (15.38)		
31–40	14 (21.54)	26 (33.33)	14.28	0.027*
41–50	13 (20.00)	26 (33.33)		
51–60	7 (10.77)	7 (8.97)		
61–70	2 (3.08)	5 (6.41)		

II. SYMPTOMS: Some reports are suggesting that the symptoms are slightly different in the case of Delta variant infection. The most common symptoms of COVID-19 were shortness of breath, cough, fever, change in sense of smell and taste, headache, nausea, vomiting, sore throat, fatigue, muscle/joint aches, and other lung complications. However, cough, loss of smell, nausea, vomiting, and diarrhea are less common with the delta variant and are still being reported in reduced quantities. For the Delta variant, the most common symptoms include sore throat, runny nose, sneezing, headache, fever, and persistent cough. A UK-based COVID symptoms tracker app 'Zoe's COVID Symptom Study' collected millions of symptom samples from fully vaccinated, single-dose vaccinated, and unvaccinated populations. For vaccinated people, the most common symptoms are headache, runny nose, sneezing, sore throat, and loss of smell. Single dose vaccinated people reported headache, runny nose, sore throat, sneezing, and persistent cough to be the most frequent manifestation of the illness. While unvaccinated people's top symptoms were headache, sore throat, runny nose, fever, and persistent cough. Therefore, headache, sore throat, and runny nose are the most reported symptoms; persistent cough is frequent in case of no/partial vaccination, fever is most frequent for unvaccinated people, and sneezing happens for fully/partial vaccinated individuals with COVID-19. There is currently no specific remedy for COVID-19 and the treatment goal is to alleviate symptoms in mild to moderate cases. Treatment is identical for the Delta variant as any other variant, and treatment should be performed based on the individual outcomes of the infected patient. Potential treatment can be devised into four categories which need to be administered at different junctures of the disease course.

III. TREATMENT

While shortness of breath, cough, and other lung issues are the most common symptoms of COVID-19, the recent variants and subvariants associate other symptoms like headache, sore throat, runny nose, and fever. Other symptoms may include fatigue, muscle or body aches, loss of taste or smell, nausea or vomiting, and diarrhea. Existing treatment for COVID should apply for Delta Plus variant cases, which should be done on a case-by-case basis. Most people who become sick should be able to recover at home by getting proper rest, staying hydrated, and taking medications (acetaminophen) to relieve fever and aches. Additionally, the FDA has approved COVID-19 and additional drugs for persons who have been hospitalized to slow the progression of COVID-19 in people who are not hospitalized but are at risk of developing severe disease. The FDA granted emergency use authorization to three monoclonal antibody treatments: a combination of casirivimab and imdevimab, a combination of bamlanivimab and etesevimab, and sotrovimab. Three monoclonal antibody treatments have emergency use authorization (EUA) by FDA, they are 1. REGEN-COV: A combination of Casirivimab and Imdevimab [18]. 2. A combination of Bamlanivimab and Etesevimab [19], and 3. Sotrovimab.These treatments are approved for non-hospitalized adults and children over age 12 with mild to

moderate COVID-19 symptoms who are at risk for developing severe COVID-19 or being hospitalized for it. These treatments must be administered intravenously as soon as symptoms appear, and they can help to lessen the likelihood of hospitalization and emergency department visits. Monoclonal antibody therapy lowered the risk of death by 20 percent in those who had not developed their antibodies against the SARS-CoV-2 virus. For people hospitalized with COVID symptoms, doctors may also use Dexamethasone, Tocilizumab, Remdesivir, Baricitinibcombined with Remdesivir, and anticoagulation drugs based on the condition of the patients. Because of the specific mutations in the Delta variant, therapeutics such as monoclonal antibody therapies may be less successful. Planas et al. compared this strain to other SARS-CoV-2 strains by testing its sensitivity to monoclonal antibodies and antibodies found in sera from people who had recovered from COVID-19 or who had received a COVID19 vaccination. Some anti-NTD and anti-RBD monoclonal antibodies, including Bamlanivimab, were unable to neutralize the Delta variant, and these antibodies had poor binding to the spike protein. They claimed that the Delta variant's propagation is linked to avoidance from antibodies that target spike protein's nonRBD and RBD epitopes. Furthermore, antibodies developed by the body in response to natural infection or a COVID-19 vaccination may not be as effective against the Delta variant as they were against the original strain.

All three treatments have been approved for the treatment of mild to moderate COVID-19 in adults and children aged 12 and up who weigh 40 kg or more and have positive results from direct SARS-CoV-2 viral testing and are at high risk of developing severe COVID-19, which could result in hospitalization or death. Note that, these are not approved for use in hospitalized patients due to COVID-19, patients requiring oxygen treatment due to COVID-19, or patients who require an increase in baseline oxygen flow rate owing to COVID-19 in those on chronic oxygen therapy due to non-COVID-19 related comorbidities [18]-[20]. REGENCOV and Bamlanivimab+Etesevimab cocktail should only be used for post-exposure prophylaxis of COVID-19 [18], [19]. These therapies ought to be given intravenously rapidly after developing symptoms and they can reduce the risk of hospitalization and emergency room visits. People who are unable to produce their antibodies against the SARS-CoV-2 virus should go through monoclonal antibody treatment which can reduce the mortality risk by 20% [16]. Because of its unique mutation, therapeutics like monoclonal antibody treatments might not be as effective on the Delta and its subvariant cases as the earlier variants. The sensitivity of the Delta strain to monoclonal antibodies and to antibodies present in sera from individuals who had recovered from COVID-19 or who had received a COVID19 vaccine have been examined and then compared this strain with other strains of SARS-CoV-2. The Delta variant indicated neutralization resistance by some anti-NTD and anti-RBD monoclonal antibodies such as Bamlanivimab while these antibodies revealed reduced adhesion to the spike protein. The authors claim that an escape from non-RBD and RBD epitopes of the spike protein targeting antibodies is affecting the rapid spread of the Delta variant. Convalescent plasma from recovered individuals can also have clinical benefits for COVID-19 patients, EUA has been granted for the use of high-titer convalescent plasma among hospitalized patients with COVID-19 who are early in the course of the disease or have impaired humoral immunity. However, as the virus strain changes, this becomes less effective. Remdesivir is the only FDA-approved antiviral drug that slows down the virus' progression and it is proven beneficial for the most acute patients of COVID-19. It is used on hospitalized patients only and it can only be intravenously administered. Dexamethasone is a steroid that proved to be very useful in severe COVID-19 patients. It is only recommended for severely ill COVID-19 patients with supplemental oxygen or ventilatory support. Data on the efficacy of Dexamethasone and other glucocorticoids showed about a 17% relative reduction in mortality for patients needing oxygen and ventilatory support but showed no conclusive benefit who did not require oxygen or ventilatory support [23]. Baricitinib, a Janus kinase (JAK) inhibitor, is commonly used in treating rheumatoid arthritis. It is believed to have possible antiviral effects besides immunomodulatory effects due to interference with viral entry. Data suggest that it might offer benefits against mortality for patients with severe diseases. It is recommended that baricitinib should be an option for high-flow oxygen or noninvasive ventilation requiring patients and for select patients on low-flow oxygen who are advancing toward requiring higher levels of respiratory support instead of dexamethasone initiation. Tofacitinib may also have similar clinical benefits, limited data suggest a lower mortality rate if it is used. For treatment of COVID-19, numerous agents that target the IL-6 pathway such as the IL-6 receptor blockers tocilizumab and sarilumab and the direct IL-6 inhibitor siltuximab have been assessed. Markedly elevated inflammatory markers (Ferritin, D-dimer) and elevated proinflammatory cytokines (interleukin [IL]-6) are related to serious and fatal COVID-19. By blocking the inflammatory pathway these agents can prevent disease progression. Tocilizumab is suggested as an option for individuals requiring high-flow oxygen or more intensive respiratory support, specifically, patients who have progressively greater oxygen requirements for only COVID19-related reasons. It is intravenously given and

showed clear benefits for fatality reduction. There are other medications with known or believed antiviral or immunomodulating effects that have been proposed for use in COVID-19 patients. Ivermectin, Hydroxychloroquine, Favipiravir, Interferons, IL-1 inhibitors, Azithromycin, Lopinavir-ritonavir, etc. are some examples of them. However, there is insufficient evidence of the clinical benefit of using these drugs, and they are not recommended to be used in COVID-19 patients without any robust clinical evidence.

IV. VACCINE EFFICACY

There have been several studies focused on the effectiveness of different vaccines against the Delta variant, a clear picture is drawn from these investigations. Current vaccines function against the original Delta variant, but show less effectiveness, especially in older age groups, since they had a slower immune response, and their protection may deteriorate faster. To estimate the efficacy of immunization against the delta variant/the predominant strain (B.1.1.7) induced symptomatic disease, they used a test-negative case-control design. After a single dose of vaccine (BNT162b2/ChAdOx1 nCov-19), efficacy was markedly lower amongst delta-infected people (30.7%) compared to the alpha-infected people (48.7%). Both vaccines resulted in analogous outcomes. The full dose effectiveness of the BNT162b2 was 93.7% for alpha-infected people while it was 88.0% for delta-infected people. The two-dose efficacy of the ChAdOx1 nCoV-19 was 74.5% for alpha-infected individuals and 67.0% for delta-infected individuals. Comparing delta against alpha, the authors concluded moderate variations in the efficacy of the vaccines after two doses. They examined the clinical attributes and consequences of 1161 hospitalized patients with COVID-19. These patients were vaccinated with COVAXIN (BBV-152) or COVISHIELD (ChAdOx1). The number of vaccinated individuals was 495 and unvaccinated individuals was 666. More than 90% of patients in these two groups have infected the Delta variant. Superior neutralizing antibodies and substantially reduced Ferritin and LDH were found in the vaccinated individuals in comparison with the unvaccinated individuals. Disease severity was 3.2% for the vaccinated group and 7.2% for the unvaccinated group. Also, the ventilatory support requirement was lower in the vaccinated group (2.8%) compared to the unvaccinated group (5.9%), although vaccinated individuals were considerably older with other risk factors. The death rate of the single dose recipient group (3.35%) was similar to the unvaccinated group (3.45%), however, death in a fully vaccinated group with breakthrough infections was almost 50% lower (1.51%). They concluded that both vaccines are beneficial to reduce illness severity and death in hospitalized patients who had been fully vaccinated against the Delta variant.

Existing immunizations are effective against the original Delta form, but they have limited efficiency in elderly age groups, especially in individuals who have not been able to establish an efficient immune response or whose protection may deteriorate more quickly. In the symptomatic Delta variant affected patients, after the first dose of Pfizer vaccine, the efficacy rate is only 36 percent while it is 30 percent after the first dose of AstraZeneca. After the second dose, this rate improved to 88 percent for Pfizer and 67 percent for AstraZeneca [23]. In a report by [24], currently authorized three COVID-19 vaccines for use in the United States showed high effectiveness in preventing laboratory-confirmed COVID-19–related hospitalizations. Among adults aged ≥65 years, the effectiveness of full vaccination with mRNA vaccines (Pfizer and Moderna) was ≥91%, and of Janssen was ≥84%. Previous studies on the Beta variant acknowledged that K417 mutations aided to evade antibodies and therefore Delta Plus may bypass vaccines and antibodies. However, there has not been enough research or data on the efficacy of vaccines against the Delta plus variants, a detailed evidence-based study with a large enough population size should be performed to determine the efficacy of the vaccines against each lineage of the Delta variant. According to CDC, vaccines are still quite successful in keeping people out of hospitals and preventing mortality against Delta and its subvariants. They said that vaccinated patients with breakthrough infections from these genotypes tend to be infectious for a shorter amount of time and recommend everyone to get vaccinated and wear masks indoors in public spaces to reduce the spread of this variant.

V. CONCLUSION

This paper concludes with little idea about the omicron variant in different aspects than previous variants. Through mutation, the virus can improve itself by infecting people or can help the virus to escape the neutralizing antibodies through mutations in the spike gene. Mutations can either weaken or strengthen the

virus enabling it to propagate faster or cause more infections. The Delta variant has a higher mutation capacity than earlier variants, leading to a high rate of spread-ability, and the complete effects and severity of the variant are yet to be unknown. The Delta variant and its lineages can transmit the disease almost twice as fast as the original strain of SARS-CoV-2, and the severity may also be greater. However, the Delta plus variants have not yet made any overwhelmingly damaging impact compared to the other variants. As more data are available on these variants, more studies are being performed to better understand the variants and their impact on the transmission, hospitalization, efficacy of vaccines, and fatality. We hope that there will be enough research on Delta Plus to successfully avoid any damaging consequence that they and their successive mutants can inflict. The above information also gave an idea about what symptoms were observed with Omicron, the effects of available vaccines, and treatment.

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