Detection Tests, Medications and Prevention Used for Managing COVID-19

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Abstract

The sudden emergence of pandemic SARS-CoV-2 has caused widespread fear and concern and has threatened global health security. The COVID-19 pandemic has revealed the weaknesses of our health systems that were unprepared to cope with a very large number of patients requiring respiratory support therapy in a short time frame. On the other hand, the pandemic has prompted the scientific community to join in efforts to fight this novel pathogen and work rigorously to find an effective vaccine of drugs against the novel coronavirus. Efforts in the short term were focused on developing vaccines that help to prevent the infection by targeting the major viral proteins such as S, E, M, N, proteins, RdRP and proteases. Trials are still ongoing to begun their effectiveness in the absence of a specific antiviral therapy against SARS-CoV-2.

In general terms, the SARS-CoV-2-related disease outbreak once again proved the existence of virus reservoirs present in wild and domesticated animals, arguing for continuous surveillance and early warning programs.

Keywords: COVID-19, SARS-CoV-2, Drugs, vaccines.

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I. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belongs to the group of Betacoronaviruses. The SARS-CoV-2 is closely related to SARS-CoV-1 and probably originated either from bats or pangolins. SARS-CoV-2 is an etiological agent of COVID-19, causing mild to severe respiratory disease or multi-organ failure[1]. The virus was first reported from the animal market in Wuhan, province of China in the month of December, 2019, and was rapidly transmitted from animal to human and human-to-human. The human-to-human transmission can occur directly or via droplets generated during coughing and sneezing [2]. Globally, around 182,319,261 million cases of COVID-19 have been registered with 3,954,324 million confirmed

deaths.The people > 60 years, persons suffering from comorbid conditions and immunocompromised individuals are more susceptible to COVID-19 infection [3].

RNA viruses represent one of the most common classes of pathogens behind human dis-eases, with around 180 currently recognized species, and around three new species discovered every. The harmfulness of these viruses is partially supported by their ability to rapidly evolve and adapt, allowing easier escape of host immune responses and quicker development of resistance towards drugs and vaccines. This ability relies on the low fidelity of viral RNA polymerases [2, 3].

Since the outbreak occurred, scientists investigated whether medications already used to treat previous viral and infectious epidemics could be effective in this case. Later last year, World Health Organization approved 6 vaccines around the world with different effectiveness [4].

II. Diagnostic and detection tests

Molecular methods and antibody serological methods are the two types of tests available (Fig.1).

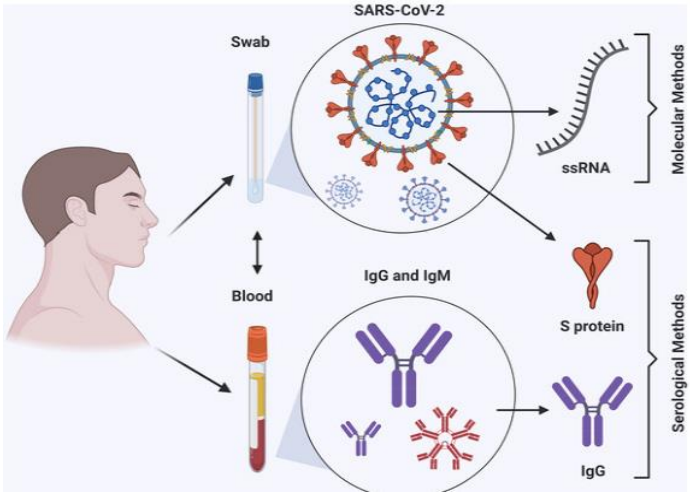

Fig. 1: Molecular and serological detect methods of COVID-19 [5].

II.1. Polymerase chain reaction test

Polymerase chain reaction (PCR) is a foundational technique in modern biological medicine. The PCR technique duplicates millions of copies of a specific piece of DNA in a sample, increasing its "visibility" and making it simpler to analyze in greater depth. PCR has allowed for significant advancements in diagnostic medicine, notably our reaction to the coronavirus [5].PCR tests are used to directly screen for the presence of viral RNA in the body before antibodies develop or signs of the disease appear. This means that the tests can detect whether or not a person is infected with the virus very early in their disease [6].

II.1.1. PCR principle

A COVID-19 PCR test is a diagnostic tool for patients who are infected with SARS-CoV-2, the coronavirus that causes the disease. PCR testing reveals if a person is infected with the SARS-CoV-

2 virus (COVID-19) and hence infectious to others. In a lab, substances known as reverse transcriptase or DNA polymerase are introduced to a nasopharyngeal sample during Covid-19 PCR testing. These substances act to replicate any viral RNA that may be present [7]. This is done to ensure that enough copies of the RNA are present to indicate a positive result, since specifically designed primers and probes bind to segments of the genetic code of interest [6]. This is critical to stop the infection from spreading further [8]. The coronavirus's RNA (ribonucleic acid) is detected via PCR.This is distinct from a COVID-19 serology (antibody) test, which identifies human antibodies. Because it is the most accurate and reliable diagnostic, the PCR test is considered the "gold standard" for diagnosing COVID-19 [9].

II.1.2. PCR test procedure

The COVID-19 PCR test has three main steps [9]:

- **Sample collection:** The respiratory material found in your nose is collected using a swab. A swab is a long, flexible stick with a soft tip that is used to clean your nose. Nasal swabs, which gather a sample inside your nostrils instantly, and nasopharyngeal swabs, which collect a sample further into the nasal canal, are two different types of nose swabs. Collecting material for the COVID-19 PCR test can be done with either type of swab. The swab is sealed in a tube and shipped to a laboratory after collection [10,11].
- **Extraction**: When a laboratory technician gets a sample, they undertake a procedure known as extraction by adding a solution known as a 'reagent' to the sample, which isolates the genetic material from the sample, including any virus that may be present [11].
- **The PCR stage** next creates millions of copies of a small amount of the SARS-CoV-2 virus's geneticmaterial using specific chemicals and a PCR machine called a thermal cycler [40 cycles]. If SARS-CoV-2 is present in the sample, one of the compounds creates a fluorescent light during the process. The PCR machine detects the fluorescent light as a "signal," and specific software is used to interpret the signal as a positive test result [2,12].

II.1.3. Meaning of PCR test results

If a patient has apositive test result indicates that he is extremely likely to be carrying SARS-CoV-2 virus. This also means that the patient is at risk from developing covid-19 and can pass the virus to others. On this case, the patient needs to seek medical counsel and follow local government guidelines, which is generally, include self-isolating for a recommended period to avoid infecting others [13].

A negative test result indicates that the most likely did not have COVID-19 at the time you took the test. However, negative PCR test results are not a guarantee that you are clear of infection; it is conceivable to be infected with SARS-CoV-2 but not have enough virus in your body to be detected by the test [5].

II.2. Lateral flow (Antigen) test (LFT)

This test looks for antigens, which are little pieces of protein on the virus's surface. Antigen testing is faster than PCR testing, requiring only 15 to 30 minutes. However, they are less accurate. Rapid antigen tests are most accurate when utilized within a few days of the onset of symptoms [9,11]. A nasopharyngeal sample is placed on a small absorbent pad and dragged down the pad through a capillary line to a strip coated with antibodies that bind to SARS-Cov-2 proteins using a Covid-19 LFT. If these proteins are present, a colored line will appear on the test, suggesting infection. If an antigen test is negative, the health care practitioner may prescribe a PCR test to confirm the negative test result because this test is not precise and accurate as PCR [6,14].

II.3. Serology test

This test determines whether you have developed an immune response to the virus (antibodies). This indicates that you'll be infected with the virus and that your body have launched an attack to combat it. Unlike PCR testing, which often employ swabs to detect Covid-19, antibody tests typically utilize blood samples [14]. This is due to the fact that, in comparison to the respiratory tract, there will be a quantity of Covid-19 virions circulating in the blood, it takes about a week for adequate antibodies to build in your bloodstream after you've been infected. As a result, this test should not be used to determine whether or not an infection is current [15].

III. Medications used for managing COVID-19

Since the outbreak occurred, scientists have been investigating whether medications already used to treat other viral infections or that could treat the symptoms of COVID-19 could be effective. Existing pharmacological trials have shown results far faster than inventing wholly new medicines from scratch [16]. Inpatient or intensive care unit medications are based on previous efficacy results in treating malaria, rheumatoid arthritis, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), Ebola, influenza, autoimmune illnesses, respiratory infections, Secondary bacterial infection, ARDS, sepsis, cytokine storm, and organ or multi-organ failure are all possible complications [17,18].

III.1. Antiviral Drugs

Antiviral medications usually target the infectious disease directly to stop it from spreading. Some medications are targeted for specific viruses, whereas others have a broad range of activity [19]. These medications were found to have antiviral properties against MERS, SARS, Ebola, influenza, and the human immunodeficiency virus. In Africa, Nigerian guidelines ban the use of all antivirals unless they are part of a clinical trial [20].

III.1.1. Lopinavir /Ritonavir (Kaletra)

Lopinavir is an antiviral protease inhibitor for systemic use in combination with ritonavir. Inhibition of human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) proteases renders

the enzyme incapable of synthesising the gag-pol polyprotein precursor, resulting in the production of immature HIV particles unable to initiate new infectious cycles. In a randomized controlled trial of COVID-19 patients admitted to the hospital [13,21]. The standard, recommended dosage for COVID-19 treatment is 400 mg lopinavir plus 100 mg ritonavir twice daily for 14 days. The medicine was found to have no advantage above usual care [22]. The Randomised Evaluation of COVid-19 therapy (RECOVERY) experiment, led by researchers at the University of Oxford, put this medicine combination to the test. According to preliminary data from the RECOVERY randomised controlled trial, the medication had little benefit for hospitalized patients [23,24].

III.1.2. Darunavir/Cobicistat (DRV/c)

When the LPV/r combination is contraindicated, this antiviral usedfor the treatment of patients infected with human immunodeficiency virus (HIV-1). Which is recommended by two guidelines (Italy and China). It is given for 5-7 days at a dose of 800 mg darunavir and 150 mg cobicistat. In July 2020, the Italian guideline, along with LPV/r, banned off-label usage of these medications [25]. This is due to a lack of data on the COVID-19 virus's combination. Darunavir's efficacy in treating COVID-19 has yet to be determined [26].

Furthermore, in China, this combination cannot be said to enhance the proportion of patients with moderate symptoms who convert to a negative polymerase chain reaction (PCR) after 5 days of treatment [27]. The final thing to consider is the drug-drug interaction profile of darunavir, notably with statin medicines (given for dyslipidemia) that can arise with long-term co-administration [28].

III.1.3. Umifenovir

Umifenovir is a long-time licensed medicine in China that was used to treat influenza virus. Umifenovir was found to not affect COVID-19 prognosis in non-intensive care units in a retrospective Chinese research [29]. In addition, stated that there is no evidence to support the use of umifenovir for enhancing outcomes in COVID-19 infected patients. For COVID-19 patients, the Chinese guideline recommended a combination treatment with LPV/r. COVID-19 patients are given 200 mg of umifenovir four times a day for five to seven days. In individuals with severe renal impairment or sinus node disease, it should be taken with caution [30,31].

III.1.4. Ribavirin

In China, the medicine is given as a 500 mg IV infusion two to three times day for 10 days, or 400 mg orally twice daily for fourteen days in Saudi Arabia and Singapore. According to the findings of a randomized, multicenter clinical trial in Hong Kong, an early triple-therapy strategy involving ribavirin, LPV/r and subcutaneous Interferon beta-1b was more successful than LPV/r alone in treating individuals with mild to moderate COVID-19 symptoms [21,32]. Early (within 7 days of the onset of COVID-19 symptoms) treatment with this triple-therapy approach is advised in China. In Singapore, after remdesivir and convalescent plasma therapy, this treatment is used as a

third-line option in severe instances or when oxygen support is required. Ribavirin causes anemia by lowering hemoglobin levels [33].The Singapore guideline recommends electroencephalogram (EEG) monitoring because anemia can aggravate any underlying heart illness and lead to myocardial infarction According to the Chinese Pharmaceutical Association, ribavirin should be avoided in the elderly population [34]. As a result, it should be avoided while pregnant. Ribavirin is mostly eliminated by the kidneys. Therefore, it can build up if you have kidney disease. According to Singapore guidelines, renal function should be checked before using ribavirin [30,35].

III.2. Anti-Malarial Drugs

Antimalarial medications hydroxychloroquine (HCQ) and chloroquine (CQ) are originally recommended to treat autoimmune illnesses. Both medications are suggested for usage in numerous COVID-19 treatment guidelines worldwide at the start of the pandemic [36]. The results of several recent research have created a quandary about the use of HCQ and CQ in the treatment of COVID-19, with some studies supporting their usage and others not, in terms of prescription alone or combination[7, 37]. Importantly, outside of clinical trials, the WHO guidelines do not encourage the use of these agents. HCQ/CQ may interact with chronic illness medications (e.g., digoxin, amiodarone, etc.) as well as COVID-19 medications (e.g., azithromycin and antiviral treatments). Because the drug's half-life is so lengthy (more than 40 days), this effect can last for several days [24, 38].

III.2.1. Hydroxychloroquine

Malaria and autoimmune diseases like rheumatoid arthritis and lupus are treated with hydroxychloroquine. The exact mechanism of antiviral activity is unknown; however, it is considered to be through viral replication inhibition [39]. Different national guidelines have established a variety of criteria for the use of HCQ in COVID-19 patients. The severity of the COVID-19 symptoms, such as the presence of dyspnea, and the patient's overall health should be evaluated before administering the HCQ [40]. In general, the medicine is advised for COVID-19 patients who are severe, confirmed, and hospitalized. Treatment with HCQ normally lasts five days, with a loading dosage of 400 mg twice day for one day and then a maintenance dose of 200 mg twice daily (or 400 mg once) for days two to five. According to published Italian SITA/SIP physicians' recommendations, depending on the severity of the case, this period can be prolonged to 20 days if necessary [25,41].

III.2.2. Chloroquine

The backbone from which HCQ was produced is chloroquine (CQ). According to many research, HCQ is more powerful and safer than CQ. CQ is commonly given as an antimalarial treatment for three days at a total dose of 1500 mg. CQ was suggested as an alternative to HCQ in several COVID-19 management guidelines but not in others: Italy, India, and Nigeria[30,42].

The 500 mg of CQ twice daily is recommended for 7 and 10 days in China and Pakistan, respectively. Before the suspension of its use in conjunction with HCQ in Belgium, the guideline recommended that 600 mg of CQ be given once, then 300 mg twice for five days [43].

III.3. Systematic Corticosteroids

The increased and uncontrolled inflammatory response caused by COVID-19 or other severe respiratory infections is one of the most serious sequelae, with symptoms ranging from mild dyspnea to ARDS, sepsis, and organ or multi-organ failure [44]. This pathological process involves several inflammatory mediators (cytokines and interleukins). Systemic corticosteroids (SCS) regulate the synthesis of proinflammatory factors and reduce the destructive immune response through their mechanism of action. Corticosteroids may have a detrimental impact despite their therapeutic potential [45]. SCS therapy is shown to increase viral load and delay viral shedding. SCS therapy is only advantageous in patients who require oxygen or who have ARDS, as proof of its effectiveness in mild instances is quite limited [37, 46].

Corticosteroid medication has a broad range of negative side effects, including immunosuppression, and it might prolong virus shedding or cause secondary infections. A low dose of 0.5–1.0 mg/kg of methylprednisolone, on the other hand, may be effective in avoiding these side effects [47]. Antibiotic prophylaxis may be beneficial in preventing subsequent infections. Dexamethasone (or other options if dexamethasone is not available) is indicated in pregnant women with COVID-19 who need all forms of supplemental oxygen in the United States [26, 48].

Other chronic conditions such as COPD, asthma, and adrenal insufficiency require corticosteroids, that were found to be useful in some COVID-19 patients who also have other chronic inflammatory disorders [43].

Dexamethasone and methylprednisolone were the most commonly prescribed corticosteroids in COVID-19 treatment guidelines. In sepsis or septic shock, hydrocortisone is safer and recommended. In the context of sepsis, however, there is no indication of efficacy differences between these medicines. Beyond clinical trials, the WHO advises against using corticosteroid medication routinely [17, 45].

Methylprednisolone is a 5 times more potent steroid than hydrocortisone.It is an intermediate-acting steroid (biological half-life: 12 to 36 hours). Synthetic corticosteroids, including dexamethasone, are used mainly for their anti-inflammatory effect. In high doses, they decrease the immune response. Their metabolic and sodium retention effect is less than that of hydrocortisone [30]. The results of a randomized multicenter trial (GLUCOCOVID) suggesting that a 6-day methylprednisolone regimen can minimize mortality, ICU

hospitalization, and the need for ventilation were reported in June 2020 (pre-print).Methylprednisolone is prescribed in doses of 40 mg (0.5 mg/kg/day) three times daily for up to seven days [14, 46].

III.4. Immune-Based Therapy

Modulators of the immune response are being investigated as supplementary therapy for COVID-19 instances that are mild to severe. Interleukin-2, alpha-interferon, gamma-interferon and monoclonal antibodies are a few examples of these agents [47]. The immune system's ability to combat infection is critical; but, in the late stages of COVID-19 infection, an intense and exacerbated immune response with catastrophic implications occurs to prevent or treat ARDS, cytokine storm, and organ failure.These drugs were employed to treat COVID-19 instances, although no evidence of such activity has yet been found. These drugs are currently being tested in clinical studies to see how effective they are against the coronavirus [31,48].

III.4.1. Tocilizumab

Tocilizumab is an interleukin-6 receptor inhibitor that is a recombinant monoclonal antibody of an IgG1 class [41]. Tocilizumab's function in the TESEO cohort and EMPACTA investigations was demonstrated.In patients with severe COVID-19 pneumonia, minimizing the danger of invasive mechanical ventilation or death. The COVACTA trial, on the other side, contradicted these results, concluding that pneumonia-associated COVID-19 patients had neither improved clinical status nor reduced death [49].

Tocilizumab is an antiviral and immunomodulatory treatment in both the early and late stages of COVID-19 infection, as well as an important medication in the cytokine storm, according to the Swiss guidelines. This drug is recommended by the Netherlands' RIVM for non-severe COVID-19 patients as well as severe COVID-19 patients who have respiratory failure or are on mechanical ventilation. Tocilizumab may also be used in patients with moderate to severe COVID-19, ARDS, or severe life-threatening cytokine release syndrome, according to Pakistani guidelines [50].

According to Chinese standards, this drug is generally administered as a starting dose of 4 mg/kg every 4 weeks, followed by an increase to 8 mg/kg every 4 weeks based on clinical response [28].

Tocilizumab dosing is based on 8 mg/kg in Switzerland and the Netherlands, with a maximum single tocilizumab dose of 800 mg and the possibility of a second dose if needed. A third dose can be taken if there is a partial or incomplete clinicalresponse, according to Italy's guidelines [51]. Tocilizumab dose for adults in Spain is depending on patient weight. Patients weighing less than 75 kg receive a single dosage of 600 mg, whereas those weighing more than 75 kg receive a single dose of 400 mg, with a second infusion given after 12 hours if analytical values relapse after partial

improvement. According to the Swiss COVID-19 treatment recommendation, tocilizumab is contraindicated in uncontrolled bacterial and fungal infections [30,43].

III.4.2. Interferon Type

Type I interferon (IFN alpha and beta) belongs to the antiviral and immune modulator medicinal groups. These are signaling proteins that, when released by virus-infected cells, boost the host's viral defense. IFN type I may control the immune response, particularly IL-6 levels, later in the disease process [52].

In COVID-19, the clinical significance of IFN's immune-regulating action is debatable. Interferon deficiency is linked to severe forms of the disease, according to one study, and IFN levels are inversely proportional to viral load [4]. However, in contrast to early therapy, late administration of IFN- or (i.e., more than 10 days after COVID-19 diagnosis) resulted with a bad prognosis of the disease, implying a pathologic effect at advanced, inflammatory stage of COVID-19[18,53].

Early IFN administration improves recovery and decreases mortality in COVID-19 patients. This positive effect of IFN is attributable to its antiviral action, emphasizing the importance of IFN administration timing. Furthermore, prophylactic IFN usage protected health-care personnel [54,55]. IFN type III preserves the antiviral activity of IFN type I but not the immunemodulation, suggesting that it could be a therapy option for viral load suppression without causing detrimentalhyperinflammation [56,57]. According to a Chinese study, combinations with different antivirals result in better results. Interferon is not recommended for COVID-19 treatment in the United States, Canada, the Netherlands (SWAB), or Nigeria unless in a clinical trial environment [18].

The use of interferon alpha 1b (5 MIU twice daily) alone or in combination with antivirals such as ribavirin and lopinavir/ritonavir was considered by the Chinese guideline. For IFN type I, Chinese recommendations advised pulmonary delivery, whereas Singapore, Malaysia, recommends subcutaneous administration [30, 58].

III.5. Antibiotics

Antibiotics are used in the treatment of upper respiratory tract infections depending on the severity of the infection and the patient health status. They are not used in the treatment of viral infections unless a subsequent bacterial infection occurs [58]. Antibiotics should not be used in minor cases (treatment or prophylaxis) or outside of hospitals, according to several guidelines. Antibiotics should only be

administered if symptoms occur exists in moderate or severe cases, according to guidelines. If the culture turns out to be negative, empiric treatment for all potential infections should be begun early using de-escalation protocols [59, 60].

During the early days of the pandemic, the use of azithromycin in the therapy of COVID-19 pandemic surfaced in an open-label non-randomized experiment in France [37]. A study started a lengthy discussion about azithromycin's function in the treatment of COVID-19 patients. Some of the reports claimed that azithromycin not only has antibacterial characteristics, but also has antiviral and immunomodulatory effects against many viruses, making it a possible COVID-19 virus therapy choice [61].

The treatment guidelines of Malaysia and France advised early empirical antibiotics such as amoxicillin /clavulanate or third-generation cephalosporins (ceftriaxone, cefotaxime or ceftaroline) in combination with azithromycin in severe COVID-19 patients [62].

In the case of azithromycin, the WHO did not list it as a therapeutic option in its recommendations. Antibiotics should not be used in light instances, according to the WHO, and prescriptions). Should only be given when serious doubts exist in intermediate casesn [45]. In severe instances, empiric treatment should be used, and antibiotic usage should be reduced in cases where cultures were negative. The Chinese authorities insisted on the rational use of antibiotics in managing COVID-19 cases [63].Based on data from animal clinical trials, France and the United Kingdom recommendations offered specific antibiotic therapy choices. Doxycycline, rather than amoxicillin, is recommended in many situations because it has a larger range, especially against mycoplasma pneumonia, which is more likely to be a secondary bacterial cause of pneumonia during the COVID-19 pandemic [15, 64].

The antibacterial properties of azithromycin are the greatest proof of its effectiveness. Despite the lack of conclusive evidence of azithromycin's efficacy in COVID-19 patients, several scientific organizations have said that azithromycin's antibacterial properties are still useful in the empirical treatment of community-acquired pneumonia CAP in COVID-19 patients [43]. All current treatment guidelines advise against using azithromycin in the treatment of CAP. The antiviral and immunomodulatory benefits of azithromycin are controversial, because it was not developed especially for COVID-19 patients [61].

III.6. Other Medications

Some medications, remedies, and vitamins have been mentioned in several guidelines, like vitamin C, zinc, vitamin D and melatonin [65].

III.6.1. Zinc and Vitamin C

Zinc has antibacterial activity, either by aiding immune cell function to combat viral infections or by inhibiting virus replication [62].

Vitamin C is an anti-oxidant that has long it's used to treat scurvy in humans. Vitamin C inhibits membrane phospholipid peroxidation and works as a free radical scavenger. It is also essential for the synthesis

of various hormones and neurotransmitters. Vitamin C lessens the duration of typical cold symptoms in adults, while the mechanism is unclear [46]. Antimicrobial and natural killer cell activity, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity are all improved when vitamin C is supplemented. Histaminemia, which was demonstrated to harm endothelial-dependent vasodilation, has been linked to vitamin C deficiency. The effect of these vitamins on allergy and inflammation, however, is still unknown [26, 65].

According to some data, combining vitamin C and zinc may help to reduce the length and intensity of cold symptoms. During infections and stress, vitamin C levels in the plasma and leukocytes drop rapidly. Antimicrobial and natural killer cell activity, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity were all observed to improve when vitamin C was supplemented. Vitamin C helps cells retain their redox integrity, protecting them from reactive oxygen species produced during the respiratory burst and the inflammatory response [65, 66].

In addition, zinc deficiency or undernutrition has been demonstrated to impair cellular mediators of innate immunity such phagocytosis, natural killer cell function, and the formation of oxidative burst. As a result, both nutrients contribute to immune function and the modification of host resistance to infectious agents, lowering the risk, severity, and duration of infectious disorders [54]. Vitamin C and zinc supplementation reduces the severity of respiratory tract infections, such as the common cold, and shortens their duration. Furthermore, vitamin C and zinc lower the risk of pneumonia, malaria, and diarrhea infections, especially in children in impoverished countries and improve their outcomes [67].

III.6.2. Vitamin D and melatonin

Vitamin D and melatonin have different cases. While there is evidence that vitamin D and melatonin may have favorable impacts on immune function, there is no proof that they have an antiviral effect. Pain, redness, heat, and swelling at the site of infection and damage are operationally described as inflammatory reactions. Mast cells are found near small blood arteries and release strong mediators implicated in allergies and inflammation when triggered [68]. Vitamin D influences tissue contraction, inflammation, and remodeling.Multiple disorders have been associated to vitamin D insufficiency, and various studies have found a close correlation between serum vitamin D levels and tissue function [69].

By impacting both innate and adaptive immunological systems, therapy targeting vitamin D_3 signaling may provide new methods for infectious and inflammatory skin diseases. Mast cells are activated by oxidized lipoproteins, resulting in increased production of inflammatory cytokines, suggesting that vitamin E may inhibit mast cell activation by reducing oxidation of low-density lipoprotein [65].

IV.Types of vaccines

IV.1. Viral vector vaccines for COVID-19

The University of Oxford/AstraZeneca vaccine uses this technology to protect against COVID-19. This vaccine transmits SARS-CoV-2 genetic material via an unrelated harmless virus (the viral

vector). When administered, our cells use the genetic material to produce a specific viral protein, which is recognized by our immune system and triggers a response. This response builds immune memory, so the body can fight off the virus in the future [27, 70].

IV.2. Genetic vaccines for COVID-19

The Moderna and Pfizer/BioNTech COVID-19 vaccines use this type of technology to train the immune system. The vaccines contain a segment of genetic material of the SARS-CoV-2 virus, which causes COVID-19 [62]. In the case of the Moderna and Pfizer/BioNTech vaccines, the genetic material, RNA, codes for a particular viral protein. When administered, your cells use the genetic material from the vaccines to make the protein, which is recognized by your immune system and triggers a specific response [49]. This response builds immune memory, so your body can fight off SARS-CoV-2 in future. The vaccine may to be restored in at a specific low temperature [70].

IV.3. Inactivated vaccines for COVID-19

This vaccine contains a killed SARS-CoV-2 virus, which the immune system recognizes and responds to without producing COVID-19 disease. This reaction strengthens immunological memory, allowing the human body to fend against SARS-CoV-2 in the future. This vaccine may need to be administered with an adjuvant to boost immune response. It is used for humans in the condition of influenza [70, 71].

IV.4. Attenuated vaccines for COVID-19

This type of vaccine contains the weakened SARS-CoV-2 virus, which is recognized by the immune system to trigger a response without causing COVID-19 illness. This response builds immune memory, so your body can fight off SARS-CoV-2 in future. It is a well-known method that necessitates time and extensive testing. It is also used in the oral polio vaccine [70].

IV.5. Protein vaccines for COVID-19

This type of vaccine contains proteins from the SARS-CoV-2 virus (harmless pieces) instead of the entire germ, which are recognized by the immune system to trigger a response. This reaction strengthens immunological memory, allowing your body to fend against SARS-CoV-2 in the future [38]. It has an excellent track record of safety and is typically taken with an adjuvant to enhance immune response. This technique is used in the Hepatitis B vaccine [70].

IV.6. Comparison between the different vaccines

There are four main types of COVID-19 vaccines that are authorized and recommended or undergoing large-scale clinical trials by world health organization [45]. Below is a description of how each type of vaccine (Table IV).

Table I: Comparison between the four main vaccines of covid19 in the world [46, 58, 66, 71].

Pfizer-BioNTech vaccine	**Moderna vaccine**	**Janssen/Johnson and Johnson vaccine**	**Sputnik V (Gam-COVID-Vac) vaccine**
mRNA vaccine.	mRNA vaccine.	Vector vaccine.	Viral Vector Vaccine.
95% effective at preventing the COVID-19 virus with symptoms.	94% effective at preventing the COVID-19 virus with symptoms.	66% effective at preventing the COVID-19 virus with symptoms.	91.6%effective at preventingthe COVID-19 virus with no serious side effects.
Food and Drug Administration (FDA) emergency use authorization.	FDA emergency useauthorization.	FDA emergency use authorization.	Some countries full and emergency authorization.
Greater than 89% effective in preventing people with health conditions, such as diabetes or obesity, from developing the COVID-19 virus with symptoms.	Greater than 90% effective in preventing people with health conditions, such as diabetes or obesity, from developing the COVID-19 virus with symptoms	Continues to be recommended by the FDA and Centers for Disease Control and Prevention (CDC) after a pause because the benefits outweigh the risk	The vaccine is well tolerated in all age groups, including older adults, as well as people with underlying conditions, who made up a quarter of total participants in the trial. These included people with diabetes, hypertension, ischaemic heart disease and obesity.
Doesn't contain eggs, latex or preservatives.	Doesn't contain eggs, latex or preservatives.	Doesn't contain eggs, latex or preservatives.	Doesn't contain eggs, latex or preservatives.
Two doses are needed, 21 days apart (or up to six weeks apart, if needed.	Two doses are needed, 28 days apart (or up to six weeks apart, if needed).	One dose isneeded.	Two doses are needed, 21 days apart.

Some protection provided after the first dose.	Some protection provided after the first dose.	Some protection provided two weeks after vaccination.	Some protection provided after the first dose.
People age 16 and older should get the vaccine.	People age 18 and older should get the vaccine.	People age 18 and older should get the vaccine.	People age 18 and older should get the vaccine.
Side effects: Injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, nausea, feeling unwell and swollen lymph node.	Side effects: injection site pain, fatigue, headache, muscle pain, chills, joint pain, swollen lymph nodes in the arm that was injected, nausea, vomiting and fever.	Side effects: Injection site pain, headache, fatigue, muscle pain, chills, fever and nausea.	side effects were: flu-like illness – headache –fatigue - injection-site reactions.
People who've had an immediate or severe allergic reaction to any of the vaccine's ingredients or after a prior dose of the vaccine shouldn't get the vaccine.	People who've had an immediate allergic reaction to any vaccine or injectable medication should be cautiousabout getting the vaccine.	People who've had a severe allergic reaction to any of the vaccine's ingredients and people who are allergic to polysorbate shouldn't get the vaccine.	People who've had an immediate or severe allergic.

IV.7. Who should not get vaccinated?

✓ If a patient has had a severe allergic reaction (anaphylaxis) or an immediate allergic reaction, even if it was not severe, to any ingredient in an mRNA COVID-19 vaccine (such as polyethylene glycol), you should not get an mRNA COVID-19 vaccine [72].

✓ If the patient experienced a severe or immediate allergic reaction after getting the first dose of an mRNA COVID-19 vaccine, he should not get a second dose of either of the mRNA COVID-19 vaccines [70].

✓ An allergic reaction is considered severe when a person needs to be treated with epinephrine or EpiPenor if they must receive medical care [66].

✓ An immediate allergic reaction means a reaction within 4 hours of exposure, including symptoms such as hives, swelling, or wheezing (respiratory distress) [69].

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