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Review

COVID 19-The Deadliest Pandemic of the Era

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Abstract

Corona virus disease 2019 (COVID-19) is caused by the SARS-CoV-2 (severe acute respiratory syndrome - Coronavirus-2). It is one of the major pandemics of 21st century that killed more than 6.6 million people worldwide. The severity of COVID-19 symptoms can range from very mild, moderate to severe. However, an infected individual may have hardly one or two symptoms, and in some cases, there are no symptoms found in positive patients. The old population is at higher risk of serious illness from COVID-19, and the risk increases with age. People who have co-morbidity also may have a higher risk of serious illness. SARS-CoV-2 is spreading from human to human by close contact, via airborne droplets generated by coughing, talking, sneezing, kissing and smooching. Direct contact between a person or patient's body fluids, such as feces, and a surface, as well as indirect contact with fomites, infection also occurs if a patient touches at infected surface and then touches his nose, eyes, mouth. Looking towards the current situation of pandemic, it is suggested that the simple cares such as washing hands with soap, use of mask, social distancing, use of sanitizers and vaccination can prevent the subsequent spread of the virus. The current review, enlighten the statistics, genome organization, structure, pathogenicity, detection techniques, antiviral drug, available major vaccine and preventive measures for the management of the deadly disease. To defeat this universal enemy, we all require national as well as global solidarity, which makes hostage to the whole world.

Keywords: Antiviral Drug, COVID-19, SARS-CoV-2, Detection, Vaccines, Prevention

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Corona virus disease 2019 (COVID-19) is caused by the SARS-CoV-2 (severe acute respiratory syndrome - Coronavirus-2).[1, 2] The first reports of it came from Asia in 2003, and they swiftly reached North America, South America, and Europe. The WHO claimed that during the 2003 SARS outbreak, 8098 people globally contracted the disease, and 744 of them passed away. Since 2004, there have been no recorded cases of SARS transmission worldwide. But is one of the biggest threats to humankind in 21st century. According to WHO (World Health Organization) report COVID19 has killed more than 7,065,880 people around the world, with 776,281,230 confirmed cases found up to 15th September, 2024.[2] America is the greatly affected continent and reported the highest number of COVID-19 confirmed cases.

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The United States of America, China, India and France occupied the top positions in confirmed COVID-19 cases (WHO., 2024; accessed on 15th September, 2024). COVID-19 has high infectivity rate and low mortality rate,[2] which has led to spread the infection across 216 countries or territories in the world (WHO, 2020). The severity of COVID-19 symptoms can range from very mild, moderate to severe. However, an infected individual may have hardly one or two symptoms, and in some cases, there are no symptoms at all (asymptomatic). The old population is at higher risk of serious illness from COVID-19, and the risk increases with age. People who have co-morbidity also may have a higher risk of serious illness.[3] MERS-CoV (Middle East Respiratory Syndrome Corona Virus) and SARS-CoV caused severe respiratory system disorders. Because of the impact of SARS, more than 7 hundred people had lost their lives in 2003.[4]

History

The first reports of it came from Asia in 2003, and they swiftly reached North America, South America, and Europe. The WHO claimed that during the 2003 SCARS outbreak, 8098 people globally contracted the disease, and 744 of them passed away. Since 2004, there have been no recorded cases of SARS transmission worldwide. But, again COVID-19 was identified in Wuhan, Hubei province of China in mid-December of 2019. It has been divulged that COVID-19 first patient was a 41 years old man who was working at the sea food market of Wuhan. COVID-19 was found to transmit from person-to-person and killed thousands of individuals instantly (A pneumonia of unknown cause reported to WHO Country office in China on 31 Dec, 2019).[5] On February 11th, 2020 the new corona virus disease (Before referred to as 2019 novel corona virus (2019-nCoV), received an official name from the WHO COVID-19 (WHO, 2020). Then International Committee on Taxonomy of Viruses (ICTV) proposed the official name of virus i.e. SARS-CoV-2 etiological agent of COVID-19.[6] The name was given because of its genetic similarity to the corona viruses responsible for the SARS outbreak in 2003. On January 30th, 2020, the WHO declared the SARS-CoV-2 as anepidemic and on 11th March, 2020 announced this outbreak as a pandemic, a public health emergency of international concern.[7, 8]

Origin of SARS-CoV-2

The virus which causes COVID-19 most probably has its ecological reservoir in bats, and the transmission of the virus to humans has likely occurred through an intermediate animal host such as a domestic animal, a wild animal or a domesticated wild animal which has been identified.[67] However, the zoonotic source of the virus is currently unknown.[2] In the end of December 2019, a pneumonia outbreak of unknown etiology took place in Wuhan, Hubei province, China, and spread quickly countrywide. The Chinese Center for Disease Control and Prevention (CCDC) identified a novel beta-corona virus called 2019-nCoV, now officially known as SARS-CoV-2;[6] MERS-CoV was thought to originate from bats.[9, 10] Both SARS-CoV and SARS-CoV-2 are interconnected and originated in bats, and most likely serve as reservoir host for these two viruses (Fig. 1).[11-15] SARS-CoV-2 shows a nucleotide sequence that has 86.9% similarity to a bat corona virus and, hence, it is suspected that it may transfer from bats to humans via intermediate host.[16, 17]

Pathogen

Corona viruses (CoVs) are known to be the largest group of viruses belonging to the *Nidovirales* order. The *Coronavirinae* contain one of two subfamilies i.e., Coronaviridae and *Torovirinae*.[18, 19] Further the *Coronavirinae* is again divided into four genera which include *alpha, beta, gamma, and delta* corona viruses. The viruses were initially sorted into these genera based on serology but are now divided by phylogenetic clustering.[20] Predominantly, Corona viruses recognize their particular receptors on the target cells through S proteins on their surface and entry to the cells results in infection. Corona virus belongs to the Coronaviridae family having positive sense RNA genome,[21] with the genome size of around 24kb-32kb, which is known to be largest in RNA viruses.[21] The name Corona virus is due to the, crown-like appearance of the surface projections. SARS-CoV-2 is grouped into the β-corona viruses, a large class of viruses that are prevalent in nature. Like other viruses, SARS-CoV-2 has many natural hosts, intermediate and final hosts. This wide host range poses unprecedented challenges for the prevention and the treatment of viral infection.[22]

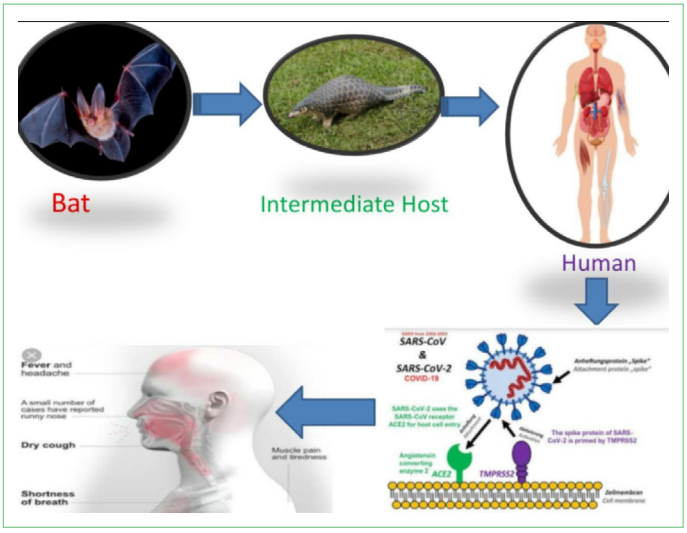

Figure 1. Transmission of SARS-CoV-2 from potential native host to Humans.

Numerous SARS- CoV-2 variants circulate in the different region of the world. The variant classified in major three categories namely Variant of Interest (VOI), Variant of Concern (VOC), and Variant of High Consequence (VOHC) [Centre for Disease Control and Prevention (CDC)]. The B.1.1.7 is also considered as UK variant and found in England; it was considered variant of concern by many workers. Similarly, Brazilian and South African variant (B.1.1.592) were also found more contagious and dangerous.[23]

Structure of SARS-CoV-2

As compared to other corona viruses, SARS-CoV-2 structure is spherical and has mushroom-shaped proteins called spikes protruding from their surface, giving the particles a crown-like appearance. SARS-CoV-2 has four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and also several accessory proteins (Fig. 2).[18] The spike or S glycoprotein (large type transmembrane protein ranging from 1,160 amino acids for avian infectious bronchitis virus) is found in the outer portion of the virus. S protein forms homotrimers protruding in the viral surface and facilitates binding of envelope viruses to host cells by attraction with angiotensin-converting enzyme 2 (ACE2) expressed in lower respiratory tract cells.[24] The spike binds and fuses to human cells, permitting the virus to gain entry. After the entry of the virus into the host cell, SARS-CoV2 binds to the ACE2 receptor that is highly expressed in the lower respiratory tract such as type II alveolar cells (AT2) of the lungs, upper esophagus and stratified epithelial cells, and other cells.[24]

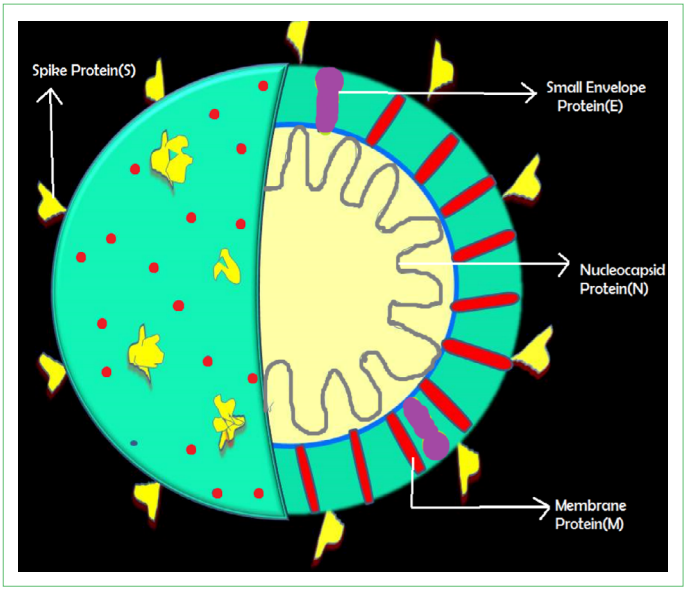

Figure 2. Diagrammatic representation of SARS-CoV-2.

Genome Organization

Genome organization is representing the linear order of elements of nucleic acid or their gene sequential arrangement. The genome (RNA; Ribonucleic acid) of the corona virus is known to be the largest among RNA viruses, approximately 27 to 30 kb. It has positive-stranded RNA, with a 5′-cap structure and 3′ poly-A tail and the diameter in the range 80 to 160 nm.[4, 18, 25, 26] The corona virus genome was elucidated on the basis of sequence relationships between subs genomic RNAs of *in-vitro* translational studies using an individual mRNA.[27] The genome and sub genome of a typical corona virus carries at least six ORFs (Open reading frames). In the genome, two third parts occupy a replicase gene that encodes the non-structural proteins and that make up only around 10kb of the total genome (Fig. 3). For the process of RNA replication and transcription, the 5' end of the genome contains a leader sequence and untranslated region (UTR), which have complex (multiple) stem loop RNA structure, which is necessary for replication and viral RNA synthesis is present at 3' UTR. Corona virus genome have 5' leader UTR-replicate- S (spike) - E (Envelope) -M (Membrane)-N (Nucleocapsid)-3' UTR-poly (A) tail with accessory gene interspersed in the structural Gene's at 3' end of genome.[18] The full genome of SARS-CoV-2 consists of 29,811 nucleotides having 8,903 (29.86%) adenosines, 5,482 (18.39%) cytosine, 5,852 (19.63%) guanines, and 9,574 (32.12%) thymine.[28] It encodes twenty-seven proteins inclusive of an RNA-dependent RNA polymerase (RdRP) and four structural proteins.[29-31] RdRP acts in conjunction with nonstructural proteins to maintain genome fidelity. A region of the RdRP gene in SARS-CoV-2 appeared to share high sequence similarity to a region of the RdRP gene found in bat corona virus RaTG13 and 96% similarity to the RaTG13 overall genome sequence.[32] The typical generic corona virus genome is a single strand of RNA, 32 kilo bases long, and is the largest known RNA virus genome. Corona viruses have the highest familiar frequency of recombination of any positive-strand RNA virus, promiscuously combining genetic information

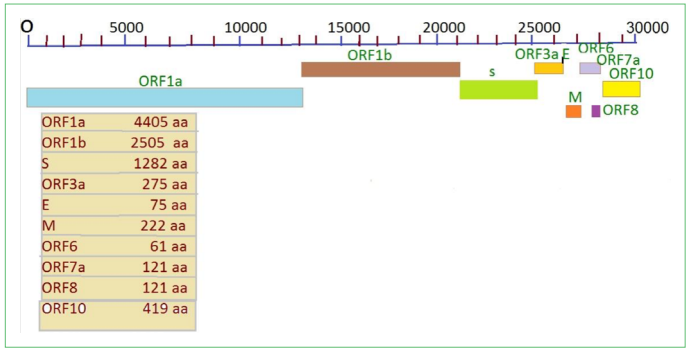

Figure 3. The diagrammatic representation of genome organization of SARS-CoV-2.

from different sources when a host is infected with multiple corona viruses. In other words, these viruses mutate and change at a high rate, which can create havoc for both diagnostic detections as well as therapy (vaccine) regimens.[33]

Entry Path of SARS CoV-2

The SARS-CoV-2 enters the body through the mouth, nose and eyes. The beginning of the infection occurs beside the attachment of spike protein to receptor ACE2of host cell. [32] The residues in the binding domain of S protein of a viral receptor strongly bind human ACE2, followed by the fusion of viral membrane and host cell. After fusion Type II transmembrane serine protease (TMPRSS2) is present on the host cell then activation of receptor and attachment of spike. Corroboration change allows the entry of viral genetic material in the host cell and now positive sense RNA is ready to be translated into proteins.[33]

Symptoms

The virus shows very high infectivity, comparatively less morbidity and can cause a wide range of symptoms and severity.[34] The most typical (quintessential) symptoms of COVID-19 are dry cough, fever, and tiredness. Additional symptoms that are uncommon and may affect some patients include body aches and pains, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell or a rash on skin or discoloration of fingers or toes.[2] As per data of Integrated Health Information Platform (IHIP) and Integrated Disease Surveillance Program (IDSP) the common symptoms reported in patient are Fever (27%), Cough (21%), Sore Throat (10%), Breathlessness (8%), Weakness (7%), Running Nose (3%), and Others (24%). These symptoms are usually mild and begin gradually increases. The infected individuals may also show very mild to moderate symptoms developed with due course of infection.[6, 17]

About 85% of the people are getting recovered from the disease without needing much health care treatment. One out of five individuals getCOVID-19 becomes seriously ill and develops difficulty in breathing. The older population, and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, or cancer, is at higher risk of developing serious illness. However, anyone can catch COVID-19 and become seriously ill. People of all ages experiencing fever and/or cough correlated with difficulty of breathing/shortness of breath, chest pain/pressure, or loss of taste, smell, speech or movement should seek medical attention immediately. If possible, it is recommended to call the health care provider or facility first, so the patient can be directed to the right ministrations.[26]

Transmission

Corona virus can be easily transmitted from person to person and has been declared as the deadliest pandemic of the year 2020 and 2021.Droplets and close contact of COVID-19 positive patients are the most common routes for the transmission of SARS-CoV-2. Respiratory infections can be transmitted by droplets of different sizes and there are two categories of the droplet, when the droplet particles are >5-10μm in diameter they are referred to as respiratory droplets, and when they are <5μm in diameter, they are referred to as droplet nuclei.[36] According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes.[37] When the infected person comes in contact with a healthy individual (within 1 meter) then the droplet infection occurs via coughing, sneezing and speaking. The droplets come in contact with the mouth, nose, and eyes are exposed to potentially infective respiratory droplets.[38]

The research workers have detected SARS-CoV-2 in samples of stool, gastrointestinal tract, saliva and urine.[16] Transmission occurs between family members including relatives and friends who intimately contact with patients and thus become conveyor of this disease. It's common to have infections among family members who share needy things with each other. In second wave of infection, it was observed that, the entire families got infected; it showed the airborne nature of the virus. It is a nosocomial transmission where infectious droplets from mouth or nose discharge are introduced to the nearby environment. If a healthy person inhales the droplet which is discharged by the infected person, then, as a result the healthy person has the chances of spreading the disease. Sources and transmission routine of SARS CoV-2 remain elusive.[39]

Furthermore, the virus is transmitted by indirect modes such as surfaces in the immediate environment such as handles of door, chairs, beds, utensils used in daily chores. It is also transmitted by the fomites (vegetables, groceries, food packet, parcels etc.). In hospitals, it can spread by the stethoscope, sphygmomanometer, thermometer and other medical instruments. Direct contact between a person or patient's body fluids, such as faeces, and a surface, as well as indirect contact with, infection also occurs if a patient touches at infected surface and then touches his nose, eyes, mouth. Open letter to the Geneva-based agency, published in the Clinical Infectious Diseases journal, 239 scientists in 32 countries outlined evidence that they say shows floating virus particles can infect people who breathe them in. Afterwards the WHO on 7th July, 2020 acknowledged "evidence emerges" of the airborne spread of the novel corona virus, after a group of scientists urged the global body to update its guidance on how the respiratory disease passes between people. Now WHO confirms the airborne transmission of virus.

Detection

In the process of detection, existence of etiological agents in the host is analyzed. Early detection is necessary to control novel infectious disease. Different types of tests are widely used for the detection of corona virus. The ideal detection method should be sensitive, specific, robust, less time consuming, low cost and easy to perform. Recently, the number of techniques are developed for the detection of SARS-CoV-2.[25] The following techniques are currently used for the detection of SARS-CoV-2.

Real Time PCR

The Real-Time polymerase chain reaction (RT-PCR) is also known as quantitative PCR. The results are observed on the instrument screen or computer screen in real time hence it is called real time PCR. There is no need for an end detection assay like electrophoresis or latter flow assay or any visual detection using dyes. The Real time PCR is most useful technique in the molecular biology laboratories and hence considered as the gold standard for the detection of the nucleic acids.[40] It is one of the most widely used laboratory methods for detecting the SARS-CoV-2. While many countries have used RT–PCR for diagnosing or identifying other diseases, such as Ebola virus and Zika virus, there is a need to support in adapting this method for the SARS-CoV-2, as well as in increasing their national testing capacities. RT–PCR has an additional step of reverse transcription of RNA to DNA, or RT, that allow for the process of amplification. This means PCR is used for pathogens, such as viruses and bacteria that already contain DNA for amplification, while RT–PCR is used for those, containing RNA that needs to be transcribed to DNA for amplification.

The availability of complete genome sequence of SARS-CoV-2 is helpful in designing primers and probes to specific testing samples collected from the individual nasal swab or by saliva (Fig. 4).[41] The viral genome is converted into DNA with the help of RNA dependent DNA polymerase (reverse transcriptase). Primers are designed uniquely to recognize complementary sequences on the SARS-CoV-2. This progress reaction is done in real time PCR and the fluorescent dye is used to intercalate with DNA and fluorescence was recorded whereas, TaqMan probe is used as in case of TaqMan (used to increase the specificity of quantitative PCR) assay.

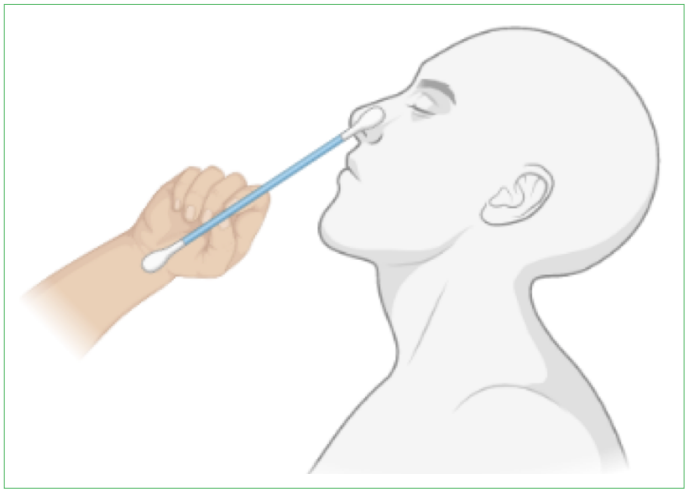

Figure 4. Sample collection for Nasopharynx.

RT- PCR is used for targeting different genomic regions of SARS CoV-2 and requires four to six hours for the detection of the SARS-CoV-2. Several primer and probe combinations were currently used by several laboratories, including an emergency use authorization (EUA)-approved assay developed by the US CDC.[34]

Serological Assay

Serology assays are the blood-based tests that can be used to identify whether people have been exposed to a particular pathogen by looking at their immune response. It detects the presence of viral proteins that are supposed to be expressed by SARS-CoV-2 in the serum and respiratory fluids. Sample taken from a person's respiratory tract by inserting a 6-inch-long swab into the cavity between nose and mouth for 15-20 seconds and again repeated on the other side of the nose, to be sure enough that the sample is collected. After that the swab is kept into a container and sent to the laboratory for testing. In serological assay, specific amount with concentration is subjected to the antibodies already immobilized on the test kit for the period of 30 minutes for detection. Although this test kit method has potential of rapid detection of pathogens, it also has drawback like false positive results and low performance. Serology tests are rapid and require limited equipment, their utility may be limited for diagnosis of acute SARS-CoV-2 infection, because it can take several days to weeks following symptom onset for a patient to mount a detectable antibody titer.[42, 43]

LAMP Based Method

Loop-mediated isothermal amplification (LAMP) is one of the PCR based detection technique that is simple, highly sensitive, specific, rapid and cost-effective DNA amplification method.[44-47] It is one of the nucleic acid-based amplification methods that do not require end detection. This method is extensively and thoroughly studied for detecting pathogens like virus, bacteria and malaria.[44, 46] LAMP method is observed to be more resistant than PCR to inhibitors in complex samples due to the use of different DNA polymerase. LAMP method employs 4 or 6 primers to binds six regions of the target DNA. Usually 60°C-65°C (constant temperature) is needed for LAMP method. Initially LAMP uses 4 primers and later on found that the addition of two loop primers can shorten half of the time required.[47, 48]

Since the SARS-CoV-2 is an RNA virus of about 30kb, single reaction of reverse transcription (RT) and LAMP, together can more crucially shorten the reaction time; therefore, a fast detection of SARS-COV-2 can be done. Therefore, a COVID-19 diagnosis kit for rapid detection of SARS- CoV-2 using RT-LAMP was developed. The limit of detection is 80 copies of the viral RNA per ml sample. In order to confirm the result of viral RNA amplification, a simple color change indication can be visualized by naked eye.[50]

CRISPR Based Assay

CRISPR is the gene editing technique that allows researchers to easily alter DNA sequences and modify gene function. It includes many potential applications like correcting genetic defects, treating and preventing the spread of diseases. This acts as a pair of 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome so that pieces of DNA can then be added or removed.

Broughton et al., 2020 develop the rapid (<40 min), easy-to-implement, sensitive and robust CRISPR–Cas12-based lateral flow assay for detection of SARS-CoV-2 from respiratory swab RNA extracts. Developed CRISPR-based detector assay provides a visual and faster alternative to the US Centers for Disease Control and Prevention SARS-CoV-2 real-time RT–PCR assay, with 95% positive predictive agreement and 100% negative predictive agreement.[51] They validated the method using contrived reference samples and clinical samples from patients in the United States, including 36 patients with COVID-19 infection and 42 patients with other viral respiratory infections.[52]

True NAT

Unlike traditional RT-PCR tests, the sample preparation in True NAT tests is fully automated, and the results are available within 30 to 55 min. The test uses nose or throat swab samples, which are collected from patients and are dipped in a solution, which is responsible for the activation of virus. Few drops of the solution are then placed on a cartridge and it is inserted into a machine, a pre-programmed reaction is initiated, which extracts the nucleic acids or the genetic material from the samples. This has to be followed by an RT-PCR. The purified nucleic acid is then added into a micro-tube containing freeze-dried RT-PCR reagents, and the solution is allowed to stand for about one minute. This solution is then applied to a microchip and the test is inserted into another machine, where the reverse transcription and PCR take place. The platform comprises a True NAT machine, in-built RNA extraction system, RT-PCR chips, collection swabs and the viral lysis medium (VLM). Single assay has a turnaround time of 35-50 minutes for 1-4 samples with a total of 12-48 samples being tested per 8 hours shift, depending upon the model of machine. TruenatTM test is a two-step diagnostic test in which first step involve E gene screening assay (True Beta CoV) for all COVID-19 suspect samples to be followed by TMnat step two for the RdRp based confirmatory test (True SARS CoV-2) in all E gene positives. True NAT is a fully indigenous or native diagnostic platform that offers a reliable and affordable option to augment SARS-CoV-2 testing capacity in India.[53] True NAT is developed by the Molbio diagnostic Pvt Ltd, India.

HRCT High Resolution CT

When it comes to the diagnosis and tracking of diseases of the lung tissue and the airways, high resolution computed tomography is a method of examination that is more accurate than chest 2-rat. A volume HRCT scan that includes the entire lung tissue is possible with modern CT technology. he COVID-19 Reporting and Data System (CO-RADS) score is a standardized system used to assess the likelihood of COVID-19 infection based on chest CT findings. The CO-RADS classification ranges from 1 to 6: CO-RADS 1 indicates a normal lung with no evidence of COVID-19 infection. This score suggests that the patient is highly unlikely to have COVID-19. CO-RADS 2 to 4 indicates a suspected COVID-19 infection. As the score increases from 2 to 4, the suspicion of COVID-19 becomes stronger based on CT findings. These scores typically suggest the presence of some abnormalities in the lungs that are consistent with a possible COVID-19 infection, though not definitive. Whereas CO-RADS 5 to 6, indicates a high likelihood of COVID-19 infection. A score of 5 suggests findings highly indicative of COVID-19, whereas a score of 6 is used when a positive RT-PCR test confirms the presence of the virus in conjunction with the CT findings.

CT Severity Score

The CT Severity Score assesses the extent of lung involvement in COVID-19 patients, providing information on the percentage of lung affected by the infection. This score is crucial in determining the severity of the disease and guiding clinical management. The scores are categorized as follows:

CT Severity Score ≤ 8: Indicates mild disease. This score corresponds to minimal lung involvement, suggesting that the patient has a less severe form of COVID-19. Patients with mild disease often require less intensive medical intervention and have a better prognosis. CT Severity Score 9 to 15: Indicates moderate disease. This score range suggests a significant but not extensive lung involvement, requiring closer monitoring and potentially more intensive treatment compared to mild cases. CT Severity Score 16 to 25: Indicates severe disease. This high score corresponds to extensive lung involvement, signifying a severe form of COVID-19. Patients with severe disease typically require intensive care, including possible mechanical ventilation, and have a higher risk of complications and mortality.

Plasma Therapy

Convalescent plasma therapy is a classic adoptive immunotherapy that has been applied for the prevention and treatment of many infectious diseases for more than a century. Plasma is often forgotten as part of blood. It makes up about 55% of the body's total blood volume. Although SARS-CoV2 had infected so many individuals, the recovery from this disease has developed immune systems with antibodies against SARS-CoV-2. After the collection of plasma from the recovered individuals, the severely infected individuals are injected with it (Fig. 5). This convalescent plasma collected from the recovered person will provide the recovery strength to the other covid-19 patients.[54]

In one of the case studies, Smriti Thakkar from Ahmedabad was the first covid-19 patient in India who volunteered to donate her plasma to treat the COVID 19 patient in a private hospital of Delhi. She claims to be a corona virus patient who helped to administer plasma therapy for the first time. The 49-year-old man who had tested positive for covid-19 on April 4th, 2020, his condition deteriorated and he was put on a ventilator support on April 8, 2020. After having plasma therapy, the ventilator support system was put off; this is a proven result about the working of plasma therapy.

Vaccines

The worldwide endeavor to create a safe and effective COVID-19 vaccine is a prime most tool to tackle with SARS-CoV-2. Vaccine should be capable of induce higher affinity neutralizing antibodies which can neutralize the SARS-CoV-2 effectively. A good vaccine must have both qualities; it must be effective as well as safe. The number of government agencies as well as private companies is in a race to develop a vaccine against covid-19. SARS-CoV-2 shares 80% and 90% of its genetic material with the virus that caused SARS, and hence it is named as SARS. Both consist of a strip of ribonucleic acid (RNA) inside a spherical protein capsule that is covered in spikes. The spikes lock on to receptors on the surface of cells lining the human lung the same type of receptor in both cases allowing the virus to break into the cell. Once inside, it hijacks the cell's reproductive machinery to produce more copies of itself, before breaking out of the cell again and killing it in the process.

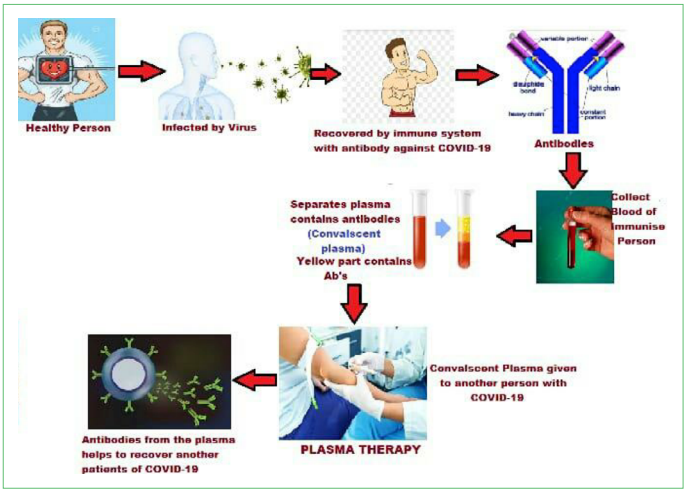

Figure 5. Diagrammatic illustration of plasma therapy.

All vaccines are based on the same basic principle to develop immunity in the host. They present modified (attenuated) part or all of the pathogen to the human immune system, usually in the form of an injection and at a low dose, to prompt the immune system and to produce antibodies against the pathogen. Antibodies and immune cells are a kind of immune memory which have been elicited once, can be quickly mobilized again if the person is exposed to the virus in its natural form. Traditionally, immunization has been achieved using live, weakened forms of the virus, or part or whole of the virus once it has been inactivated by heat or chemicals. Also, these methods have some drawbacks. The live form can continue to evolve in the host, for example, potentially recapturing some of its virulence and making the recipient sick, while higher or repeat doses of the inactivated virus are required to achieve the necessary degree of protection. Some of the Covid-19 vaccine projects are using these tried-and-tested approaches, but others are using newer technology.[55] Upto 08.05.2021fourteen vaccines got approved for immunization against Covid-19. Bellow mentions the details of the approved vaccines.

Indian Vaccine; ICMR/Bharat Biotech

Indian council of Medical Research (ICMR), National Institute of Virology (NIV) and Bharat biotech international limited (BBIL) together were expecting to launch the first COVID-19 vaccine (COVAXIN) in the country. COVAXIN®, India's first indigenous COVID-19 vaccine. The vaccine is an imperative SARS-CoV-2 strain that had been isolated by NIV, Pune, received from ICMR after which it was further developed into a vaccine at Hyderabad based Bharat Biotech Pvt. Ltd. The vaccine is developed using Whole-Virion Inactivated Vero Cell derived platform technology. Inactivated vaccines do not replicate and are therefore unlikely to revert and cause pathological effects. They contain dead virus, incapable of infecting people but still able to instruct the immune system to mount a defensive reaction against an infection. It is a 2-dose vaccination regimen given 28 days apart (Bharat Biotech Website). COVAXIN® is approved in the 9 countries (Covid Vaccine Tracker). Inactivated vaccines have a well -proven record and Bharat biotech also has an immense knowledge in inactivated vaccines for many diseases like Polio, Japanese encephalitis, rabies, Chikungunya, Zika and now for SARS -CoV-2.[56]

Sputnik V Vaccine

Sputnik V is the first approved vaccine against COVID-19 in the world developed by the Russia, is a milestone in the global efforts to protect people against corona virus. It is developed by Gamely Research Institute in Russia and the Health Ministry of the Russian Federation. Sputnik V not only w protects people, but it will also help to recover the global economy, it is based on the already existing human adenoviral-vector platform where inactivated adenoviruses act as vectors or vehicles, delivering genetic material from S-protein, which forms the spike of corona virus into a human cell to induce an immune response. Sputnik V is administered in two doses 21 days apart; however, a representative from Gamely indicated it could be possible to increase the amount of time between doses to up to 3 months (Regulatory Affairs Professionals Society (RAPS) Rockville, MD 20852). It is an Approved in 65 countries and currently 19 trials are carried out in the 6 countries.[57, 58]

Moderna

The American (Massachusetts-based) Biotech Company Moderna Inc. developed an RNA-based vaccine, which is being known as mRNA-1273. The mRNA vaccines are shown as an alternative approach to the traditional vaccines. The RNA-based vaccine works by carrying the molecular genetic code to make the protein which is known as the mRNA sequence. This sequence instructs the human cells to build viral proteins to fight the virus. As a result, the body's immune system gears up to fight the virus. The vaccine candidate mRNA-1273 carries the mRNA strand of the spike protein of the novel corona virus, which will be used by the human cells to produce the antigen required to fight the virus, just by using the genetic information of a specific protein.[56]

The company had already successfully completed phase I and Phase II trials of its vaccine candidate. Thevaccine is being developed in collaboration with the Moderna Inc and National Institute of Allergy and Infectious Diseases (NIAID) collaboratively developing the potential mRNA-1273 vaccine. In the press release of June 11, 2020 Moderna has finalized the Phase II study protocol based on feedback from the U.S. Food and Drug Administration (FDA). The randomized, 1:1 placebo-controlled trial is expected to include approximately 30,000 participants enrolled in the U.S. and is expected to be conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The vaccine candidate was also granted a 'fast track' designation by the FDA and the company is slated to begin phase 3 trials in the month of July, 2020. This vaccine is approved in 45 countries and presently 17 trials are ongoing in 3 countries (Covid Vaccine tracker).[57, 58]

AstraZeneca

AstraZeneca and the Oxford Vaccine Group at the University of Oxford have developed COVID-19 Vaccine AstraZeneca (Vaxzevria in Europe; previously AZD1222 and ChAdOx1), a chimpanzee adenovirus vaccine. In India, it is jointly developed by the Serum Institute of India and AstraZeneca and goes by the name Covishield. The vaccine is administered in two doses, between 4-12 weeks apart. The vaccine increased levels of both protective neutralizing antibodies and immune T-cells that target the virus. The results published in the Lancet medical journal states that it is a key milestone for one of the fastest-moving vaccine projects globally.[45] This is the one of the most leading vaccine developed for the prevention of this deadly pandemic. The AstraZeneca trials are funded in part by BARDA and OWS. OWS has allocated $1.6 billion for AstraZeneca, which includes $1.2 billion for 300 million doses of the vaccine and as well as research and clinical testing. AstraZeneca is approved in highest 98 countries and the 25 trials in 15 countries.[57, 58]

Johnson & Johnson

Janssen Biotech, a company owned by Johnson & Johnson, has developed COVID-19 Vaccine Janssen (formerly JNJ-78436735 and Ad26.COV2. S), a single-dose COVID-19 vaccine, using their AdVac and PER.C6 systems, which were also used to develop the company's Ebola vaccine. COVID-19 Vaccine Janssen is a part of Operation Warp Speed. [47] Johnson and Johnson pharmaceutical company is planning with the National Institute of Allergy and Infectious diseases for a final stage trial in mid-September, ahead of its original schedule if the early studies go well.[48] Johnson and Johnson are also using the same technology to make Ebola vaccine, which won European regulatory approval late last month.[49] The company commits to invest more than $1 billion in fighting the corona virus. This vaccine is approved in the 41 countries 8 trials in 17 countries.[57, 58]

Inovio

Inovio is a biotechnology company which is the first and only company to have clinically demonstrated that a DNA medicine can be delivered directly into cells in the body via a proprietary smart device to produce a robust and tolerable immune response. For the vaccine of corona virus, Inovio is using technology where virus Gene's is injected into a piece of DNA.[57, 58] One of the main features of Inovio's DNA vaccines have the ability to generate balanced antibody and T cell immune responses, which in the case of SARS-CoV-2 infection could be more important in the development of potential COVID-19 vaccines. In this regard, recent scientific reports have highlighted that SARS-CoV-2-specific T cells found in convalescent patients have been

positively implicated in controlling the severity of their COVID-19 disease while other studies have shown that a significant proportion (33% to 40%) of convalescent individuals in their reports had neutralizing antibody below detectable levels.[54] Inovio received $10 million from Bill Gates,' Coalition for epidemic preparedness innovation ' to accelerate testing of device.[57, 58]

Cansino

China based company Cansino, made corona vaccine using a genetically engineered adenovirus, called adenoviral vector, to deliver the gene that encodes the SARS-CoV-2 spike protein into human cells. Cansino measured the concentration of neutralizing antibodies that prevented the virus.[55] Cansino vaccine found to be safe and effective in generating an immune response against SARS-CoV-2 in humans in phase I trials, Ad5-nCoV was among the China's leading candidates for vaccine of corona virus for quite some time. According to the reports of the media, it was the first in the world to begin clinical trials on March 16, 2020. CanSino had conducted phase I and II trials in Wuhan, the origin of the corona virus outbreak. This vaccine is approved in 5 countries, currently conducting 8 trials in 6 countries.[57, 58]

Control of COVID-19

Till date, no perfect drug is available for the treatment COVID-19. Antiviral drugs are one of the remedies used for the treatment of viral diseases. Most antiviral drugs are prepared to target specific viruses, whereas a broad-spectrum antiviral is effective against a broad range of viruses. Numbers of drugs are now used against SARS-CoV-2, but still humanity is waiting for the perfect magic bullet against the virus.[57] Only supportive therapy is the treatment strategy followed by health professionals. Supportive therapy is based on the symptoms which include antipyretic and analgesic, maintenance of hydration, mechanical ventilation as respiratory support and uses of antibiotics to prevent the bacterial infections. In emergencies the following antiviral drugs are used for the treatment of severe Covid-19 patients.[58]

Remdesivir

It is correlated with research in MERS and found that it blocks the virus replication machinery. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination.[62] Remdesivir has been reported as one of the most promising antiviral drugs against a wide array of RNA viruses. It was reported that Remdesivir treated COVID-19 patient achieved good results. Xiao et al. found that Remdesivir was effective in the control of COVID-19 in vitro[61] Emergency Use Authorization (EUV) of Remdesivir may be considered only in the patient with: Moderate oxygen to sever disease and No Renal or Hepatic dysfunction and person having symptoms from10 days Recommended Dose of 200mg IV followed by 100mg IV OD for 4 days.

Chloroquine

Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug. Chloroquine is known to block the virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV-2.[61] Wang et al., 2020 revealed that, time-of-addition assay demonstrated that chloroquine functioned at both entries, and at post entry stages of the SARS-CoV-2 infection in Vero E6 cells. Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is widely distributed in the whole body, including lung, after oral administration.[61, 62]

Favipiravir

Researchers found that, it is helpful against covid-19. It is an antiviral used for treating influenza patients and particularly inhibits or obstructs the RNA polymerase which plays a vital role in viral replication. In India, a phase 3 trial combining 2 antiviral agents, favipiravir and umifenovir, had been started in May 2020.[63]

Arbidol

It also works against viral infections and it is an anti-influenza drug that targets the viral hemagglutinin (HA), is used in a clinical trial against COVID-19. Apart from the influenza virus, it was reported that Arbidol inhibits a wide array of viruses by interfering with the multiple steps of virus replication cycle.[64] On other hand Lopinavir/ Ritonavir, is commonly sold under the Brand named Kaletra. Ritonavir increases the levels of lopinavir and this helps lopinavir to work superior and better. It is the fixed dose combination work used for the treatment and prevention of HIV/AIDS. Bin Cao, M.D., et al, 2020[65] in trial found that in hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit. The team of research workers at the King George's Medical University has found that ayurvedic medicines and home remedies like turmeric, neem and tulsi not just build immunity against diseases, but may also, to an extent, block novel corona virus from affecting a person's body.[65]

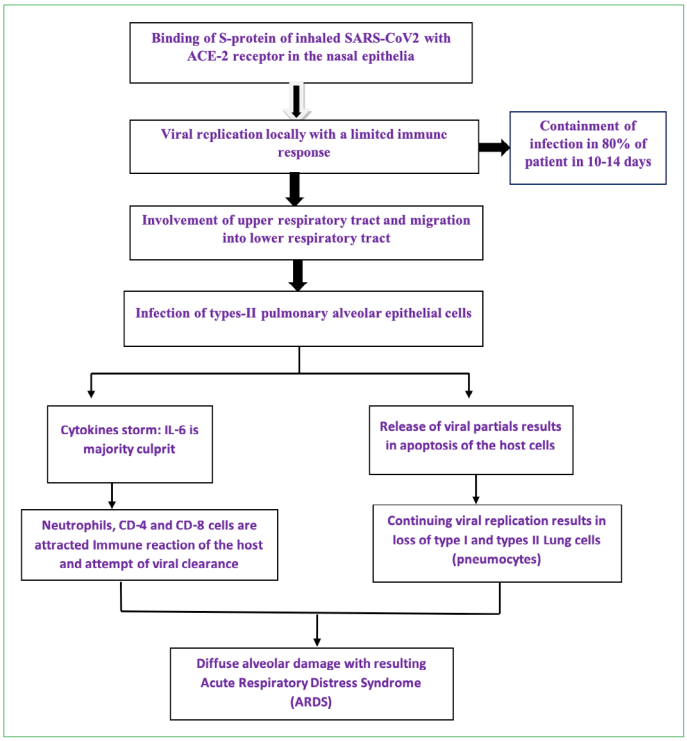

Figure 6. Pathophysiology of SARS-CoV-2.

Tocilizumba

Corticosteroids and tocilizumab injection are being investigated for the treatment of COVID-19 in patients who need extracorporeal membrane oxygenation, supplemental oxygen, or a ventilator (ECMO; a device that adds oxygen to the blood). In order to distribute tocilizumab injectable to treat some adults and kids aged 2 and older who are hospitalized with a COVID-19 infection, the FDA has issued an EUA. Presence of sever disease (preferably within 24-48 hours of onset of sever disease/ICU admission.).

Preventive Measures

WHO provides so many guidelines to deal against this deadly virus. Regular washing of hands in interval of time with soap, use of hand sanitizer, use of mask, social distancing, avoid touching and facial areas like nose, mouth, eyes and some other respiratory hygiene practices and only take only those medicine which are prescribed by doctors.

Use of Washing Soap

Soap micelles carry two sides, head part and tail part where head part is hydrophilic and tail part is hydrophobic. A very important role played by the tail, in which tail have affinity for the lipid molecule on the outer covering of the virus body which is made up of liquid only. Tail tends to insert in the liquid and have a “crowbar" effect on the envelope that breaks the lipid envelope. This still is also capable of taking bond between RNA (genetic material of virus) and Lipid envelope.

Alcohol Based Sanitizers

Alcohol changes the shape or denatures the spikes that are present over the body of the virus which is usually made up of proteins alcohol-based sanitizer also perform a job like soap.

Use of Mask

The use of masks will reduce the transmission of droplets from infected to healthy people as this is majorly focused as the respiratory disease. It also helps[66] reduce the chances to touch our hands to our mouth, nose and eyes. Write about N95 masks.

Social Distancing

Initially, the WHO suggested that at least six feet distance between people to person may prevent oneself from small droplets that are discharged by the infected person into the environment. But currently looking at the airborne nature of virus as declared by WHO and CDC, six feet’s distance would not be sufficient to prevent from the virus. Hence, wearing of the mask will be effective for both effected and the unaffected ones both.

Avoid Touching Eyes, Nose and Mouth

In order to reduce the risk of virus entering into our body, highly exposed area of our body i.e, eyes, nose and mouth should be protected. Usually, our hands touch these parts, so it is necessary to avoid touching such areas.

Respiratory Hygiene Practices

Use tissue or handkerchiefs while sneezing or coughing should be practiced. After doing such things, tissue papers should be thrown or disposed off in the dustbins.

Personal Protective Equipment

Personal protective equipment’s, commonly referred to as "PPE", is a special type of equipment worn by the doctors, nurses, diagnostic staff, medical housekeeping staff, the personnel involved in the cremation or anyone who handles the Covid-19 positive case to minimize exposure of SARS-CoV-2. PPE includes gloves, mask, and gown. Since, later it was found to be an airborne, then face protection (goggles and mask or face shield), gloves, gown or coverall, head cover, rubber boots (WHO)were recommended.[67] The need for continued emphasis on hand hygiene was also revealed. A barrier for improving the hand hygiene compliance rates is the belief that gloves can make hand hygiene unnecessary.

Lockdown

Lock down is the step taken by the government of different countries for the safety of public of that particular area. Essential services like groceries, petrol pumps, banks are kept opened depending upon the severity of disease. The

slogan given by the Indian government is "stay home, stay safe", but number of countries like India, Russia, China, Japan strictly imposed the lockdown rules in the first wave and as a result these countries were able to manage virus in much extents. Whereas, some countries like Italy, Spain, Britain and America initially did not imposed strict lockdown, hence, infection spread very fast and resulted in high number of deaths were reported in these countries.

Conclusion

A combination of antiviral drugs with Hydroxychloroquine, Azithromycin, Favipiravir and many other remedies under trial (with the consultation of a medical practitioner) will serve as the best option to treat the patients, depending on the patient's conditions and symptoms. These drugs are used against mild to moderate symptoms patient. Some of the above drugs like Remdesivir and Favipiravir also got the emergency approval. SARS-CoV-2 is spreading among humans by close contact, via airborne droplets generated by coughing, talking, sneezing, kissing and smooching. Looking towards the current situation of pandemic, it is suggested that, simple cares such as washing hands with soap, use of mask, use of sanitizers, social distancing and vaccination can prevent the subsequent spread of the virus. To defeat this universal enemy, we all require national as well as global solidarity, which makes hostage to the whole world.

Disclosures

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