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Unveiling mysteries of CoVID19

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Abstract
Coronavirus is a major health concern of the entire world at present devouring millions of lives fighting against it. It is one of the major pathogens that primarily target the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV, characterized as agents that pose a great public health threat. In late December 2019, a series of patients were admitted to hospitals with a provisional diagnosis of pneumonia of an unknown etiology, who were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China. Early reports predicted the onset of a potential Coronavirus outbreak given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus(COVID-19, named by WHO on Feb 11, 2020) which was deemed to be significantly larger than 1 (ranges from 2.24 to 3.58).At the moment, supportive measures and prevention by controlling the spread of infection is the best therapy against the viral infection.
In our fight against this virus so many questions came into light like: Is it man made? Why it is getting tougher to get a vaccine? Any new mutated forms of virus arose? Will it reinfect? Any role of passive immunisation? --

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I. Introduction

According to the World Health Organization (WHO), viral diseases continue to source aserious issue to public health such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, H1N1 influenza in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.

An epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on December 31, 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. Because of the inability to identify the causative agent, these first cases were classified as "pneumonia of unknown etiology." The Chinese Centre for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation program. The etiology of this illness is now attributed to a novel virus belonging to the coronavirus (CoV) family.[1]

On February 11, 2020, the WHO Director-General, Dr.TedrosAdhanomGhebreyesus, announced that the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019".

The new virus evolved to be contagious causing quick global transmission. Initially, the virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus due to similarity with the one that caused the SARS outbreak (SARSCoVs).

Prevalence

The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died. By January 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension, and cardiovascular disease. These patients were presumed to have nosocomial infection. It was concluded that the COVID-19 is likely spread due to many patients getting infected at various locations throughout the hospital through unknown mechanisms. Moreover, only clinically sick patients were tested leaving the question of affected asymptomatic individuals.

The first case of human-to-human transmission of COVID-19 was reported in the US on January 30, 2020. Globally, the number of confirmed cases has reached 20lakhs in 210 countries as on 15 April 2020[2].

The most up-to-date source for the epidemiology of this emerging pandemic can be found at the following sources:

The WHO Novel Coronavirus (COVID-19) Situation Board.

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The Johns Hopkins Centre for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

Pathophysiology

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV)[3]. Genetic constitution reveals that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. SARS-CoV-2 belongs to the betaCoVs category. It is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.The pathology of pneumonia seems to be complex. Clinical and preclinical research are yet to explain many aspects that underlie the specific clinical signs of the disease. The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. The effect is extensive tissue damage. IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer. It is also suggested in the pathogenesis of the cytokine release syndrome (CRS), an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

The severe symptoms of COVID-19 are associated with an increasing number and rate of fatalities. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines.

Histopathology

Tian et al. and others reported histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found to have had the infection at the time of surgery[4]. Apart from the tumors, the lungs of both cases showed edema and important proteinaceous exudates as large protein globules. Vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes were noted.

Appearance

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. The genomic structure is organized in a +ssRNA of approximately 30 kb in length — the largest known RNA viruses — and with a 5′-cap structure and 3′-poly-A tail. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.There are spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors.

Transmission

Based on the large number of infected people that were exposed to the wet animal market in Wuhan City where live animals are routinely sold, it is suggested that this is the likely zoonotic origin of the COVID19. Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual as the lung epithelial cells are the primary target of the virus. Gastrointestinal involvement of SARS-CoV-2 infection and isolation of SARS-CoV-2 from fecal samples of patients are in support of the importance of fecal–oral route in SARS-CoV-2 transmission.

Signs & symptoms

The COVID-19 may present with mild, moderate, or severe illness.The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia. Among the severe clinical manifestations, there are severe pneumonia, ARDS, sepsis, and septic shock. The incubation period seems to be dependent on the age of the patient and status of the patient's immune system.

Clinical history of the patient manifests fever, which is not very responsive to antipyretics, and a state of malaise often associated with a dry cough. After 5-7 days, older patients with already impaired lung function begin to experience shortness of breath and increased respiratory rate followed by a rapid deterioration of respiratory functions. COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat and intestinal symptoms like diarrhoea.

Diagnosis

Most patients with confirmed COVID-19 have presenting fever and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing).

Specimens are collected from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage.RTPCRbased SARS-CoV-2 RNA detection in respiratory samples provides the only specific diagnostic test at the initial phase of the outbreak[5,6].

In the early stage of the disease, a normal or decreased total white blood cell count and a decreased lymphocyte count can be demonstrated. Lymphopenia appears to be a negative prognostic factor. Increased values of liver enzymes, LDH, muscle enzymes, and C-reactive protein can be found. There is a normal procalcitonin value. In critical patients, D-dimer value is increased, blood lymphocytes decreased persistently, and laboratory alterations of multiorgan imbalance (high amylase, coagulation disorders, etc.) are found.If the test result is positive, it is recommended that the test is repeated for verification. In patients with confirmed COVID-19 diagnosis, the laboratory evaluation should be repeated to evaluate for viral clearance prior to being released from observation.ELISA kits for detection of IgM and IgG antibodies against N and other SARS-CoV2 proteins have also been available more recently[7,8.]

Management

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available. The treatment is symptomatic and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be indicated in cases of respiratory failure refractory to oxygen therapy and hemodynamic support for managing septic shock. Non-invasive techniques can be used in nonsevere forms of respiratory failure[9]. Systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) are not recommended. Steroids can only be used when SARS-CoV-2 has already been eliminated by human immune response.Inappropriate administration of antibiotics should be avoided.

Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (e.g. 5 million units by aerosol inhalation twice per day) is also used.

Preclinical studies suggested that remdesivir (GS5734) — an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola — could be effective for both prophylaxis and therapy of HCoVs infections[10].This drug was positively tested in a rhesus macaque model of MERS-CoV infection[11].

Plasma therapy

Patients who have recovered from COVID-19 with a high neutralizing antibody titer may be a valuable donor source of convalescent plasma therapy.Nevertheless, the potential clinical benefit and risk of convalescent blood products in COVID-19 remains uncertain. Kai Duan ET AL., performed this pilot study in three participating hospitals to explore the feasibility of CP treatment in 10 severe COVID-19 patients[12].

Prevention

The most important strategy to undertake is to frequently wash hands and use portable hand sanitizer and avoid contact with face and mouth after interacting with a possibly contaminated environment.Healthcare workers caring for infected individuals should utilize contact and airborne precautions including PPE such as N95 or FFP3 masks, eye protection, gowns, and gloves to prevent transmission.

The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen the application of strict hygiene measures for the prevention and control of infections.The public services and facilities should provide decontaminating reagents for cleaning hands on a routine basis.
- Individuals who are immunocompromised, should avoid public gatherings.

Differential Diagnosis

As early stages of the disease are nonspecific, differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g., vasculitis, dermatomyositis) common respiratory disorders such as Adenovirus, Influenza, Human metapneumovirus (HmPV), Parainfluenza, Respiratory syncytial virus (RSV), Rhinovirus (common cold).

Unveiling some mysteries beneath covid19 Is it man-made?

Much debate is being made regarding the origin of corona virus. Is the virus a natural disaster or a manmade weapon is still a trending question.Viral infections commonly involving animals may undergo mutation and follow human beings. The first known severe illness caused by a coronavirus happened with the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic in China. A second outbreak of severe illness began in 2012 in Saudi Arabia with the Middle East Respiratory Syndrome (MERS).

According to the World Health Organization, during previous outbreaks due to other coronaviruses, human-to-human transmission occurred through droplets or objects making contact, suggesting that the transmission mode of the 2019-nCoV can be identical.

Diseases spreading from animals to humans are called zoonotic diseases,often rare. The chief concern with them is that since they are new to humans, the human body does not have any immunity to them. It is believed to have originated in a seafood market in Wuhan that was involved in the illegal sale of wildlife. According to WHO, wherever there is close mixing of humans and animals, especially the unregulated handling of blood and other body products, as happens for example in China‘s animal markets, there are greater chances of transmission of a virus from animals to humans, and its mutation to adapt to the human body.

The novel SARS-CoV-2 coronavirus that emerged in the city of Wuhan, China, last year and has since caused a large scale COVID-19 epidemic and spread to more than 100 other countries is the product of natural evolution, according to findings published in the journal *Nature Medicine*.The analysis of public genome sequence data from SARS-CoV-2 and related viruses found no evidence that the virus was made in a laboratory or otherwise engineered.

The zoonotic origin of the COVID-19 is attributed to the large number of infected people exposed to the wet animal market in Wuhan City where live animals are routinely sold.Cases that occurred within families and among people who did not visit the wet animal market in Wuhan suggest human transmission. Person-toperson transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual. The binding of a receptor expressed by host cells is the first step of viral infection followed by fusion with the cell membrane. It is reasoned that the lung epithelial cells are the primary target of the virus.

"By comparing the available genome sequence data for known coronavirus strains, we can firmly determine that SARS-CoV-2 originated through natural processes," said Kristian Andersen, PhD, an associate professor of immunology and microbiology at Scripps Research and corresponding author on the paper.[13]

Shortly after the epidemic began, Chinese scientists sequenced the genome of SARS-CoV-2 and made the data available to researchers worldwide. It has shown that Chinese authorities rapidly detected the epidemic and the number of COVID-19 cases have been increasing because of human to human transmission after a single introduction into the human population. Andersen and collaborators at several other research institutions used this sequencing data to explore the origins and evolution of SARS-CoV-2 by focusing in on several telltale features of the virus.

The scientists analyzed the genetic template for spike proteins. They focused on two important features of the spike protein: the receptor-binding domain (RBD) that grips onto host cells, and the cleavage site a that allows the virus to enter host cells.

The scientists found that the RBD portion of the SARS-CoV-2 spike proteins had evolved to effectively target a molecular feature on the outside of human cells called ACE2, a receptor involved in regulating blood pressure. The SARS-CoV-2 spike protein was so effective at binding the human cells, in fact, it was concluded as a result of natural selection and not the product of genetic engineering.

In genetic terms, Chan et al. have proven that the genome of the new HCoV, isolated from a clusterpatient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-likeCoVZXC21 and 82% with that of human SARS-CoV. These genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. Since the mutation in the original strain could have directly triggered virulence towards human, there is a question of any intermediary.

This evidence for natural evolution was supported by data on SARS-CoV-2's backbone -- its overall molecular structure. To innovate a new coronavirus as a pathogen, it has to be made from the backbone of a known pathogenic virus. But the scientists found that the SARS-CoV-2 backbone differed substantially from those of already known coronaviruses and mostly resembled related viruses found in bats and pangolins.

Josie Golding, PhD, epidemics lead at UK-based Wellcome Trust, said the findings by Andersen and his colleagues are "crucially important to bring an evidence-based view to the rumors that have been circulating about the origins of the virus (SARS-CoV-2) causing COVID19."[14]

"They conclude that the virus is the product of natural evolution," Golding adds, "ending any speculation about deliberate genetic engineering."

The possible answers for the most likely origins for SARS-CoV-2 are as follows.

The virus evolved to its current pathogenic state through natural selection in a non-human host and then to humans. This is how previous coronavirus outbreaks have emerged, with humans contracting the virus after direct exposure to civets (SARS) and camels (MERS). The researchers proposed bats as the most likely reservoir for SARS-CoV-2 as it is very similar to a bat coronavirus. An intermediate host was likely involved between bats and humans as no cases of direct bat-human transmission are reported.Here, both of the distinctive features of SARS-CoV-2's spike protein -- the RBD portion that binds to cells and the cleavage site that opens the virus up - would have evolved to their current state prior to entering humans. This explains the rapid spread of infection among human beings owing to its pathogenic potential[15].

On the other side, a non-pathogenic version of the virus from an animal host entered humans and then evolved to its current pathogenic state within the human population. For instance, some coronaviruses from pangolins, armadillo-like mammals found in Asia and Africa, have an RBD structure very similar to that of SARSCoV-2. A coronavirus from a pangolin could possibly have been transmitted to a human, either directly or through an intermediary host such as civets or ferrets.Then the other distinct spike protein characteristic of SARS-CoV-2, the cleavage site, could have evolved within a human host, possibly via limited undetected circulation in the human population prior to the beginning of the epidemic. The researchers found that the SARS-CoV-2 cleavage site, appears similar to the cleavage sites of strains of bird flu that has a rapid among humans. A virulent change in human cells might have emerged and caused a pandemic[16].

The specific origin of the virulent nature remains uncertain. If the transmission is from an infected animal, then there is a serious challenge of future outbreaks as infected animals can still be present. If the nonpathogenic form is the animal source, then there are less chances of a global spread. For reasons yet to be explained, these viruses can cross species barriers infect humans.

Two parental viruses of SARS-CoV-2 have now been identified. The first one is bat coronavirus RaTG13 found in Rhinolophusaffinis from Yunnan Province and it shares 96.2% overall genome sequence identity with SARS-CoV-2. The second one is a group of betacoronaviruses found in the endangered species of small mammals known as pangolins, which are often consumed as a source of meat in southern China[17.] They share about 90% overall nucleotide sequence identity with SARS-CoV-2 but carries a receptor-binding domain predicted to interact with ACE2 and sharing 97.4% identity in amino acid sequence with that of SARS-CoV-2. They are closely related to both SARS-CoV-2 and RaTG13, but apparently they are unlikely the immediate ancestor of SARS-CoV-2 in view of the sequence divergence over the whole genome. Many hypotheses regarding recombination, convergence and adaptation have been put forward to suggest a possible emergence of SARS-CoV-2, yet direct evidence is lacking. What animals might serve as reservoir and intermediate hosts of SARS-CoV-2 is to be probed. Although Huanan seafood wholesale market was suggested as the original source of SARS-CoV-2 and COVID-19, there is evidence for the involvement of other wild animal markets in Wuhan.

Can there be a human ‗super-spreader' in the Huanan market need to be evaluated. The origins of SARS-CoV-2 and COVID-19 need to be unveiled by further investigations but for now as there is no evidence of its laboratory origin we can conclude it that covid19 has been evolved through natural selection .

Why there is no vaccine yet?

As the saying goes, ‗Prevention is better than cure', there is an urgent need for invention of vaccines against covid19. The number of affected individuals is rising at an alarming rate and a vaccine has the utmost potential for targeting the virus and control of the pandemic. Effective vaccination could play a significant role in curbing the spread and to eliminate it from the human population. Better understanding of this new virus is mandatory. Scientific efforts to address this challenge are still in infancy. Much remains to be learnt about the

virus, its biological properties, epidemiology, etc. Atpresent, there is a lack of information about specific immune responses against SARS-CoV-2, which pose a challenge for vaccine development.

By screening the experimentally-determined SARS-CoV-derived B cell and T cell epitopes in the immunogenic structural proteins of SARS-CoV, a set of B cell and T cell epitopes derived from the spike (S) and nucleocapsid (N) proteins that map identically to SARS-CoV-2 proteins was found. As no mutation has been observed in these identified epitopes among the 120 available SARS-CoV-2 sequences, immune targeting of these epitopes may provide a solution.

Worldwide collaborative efforts from scientists pave way to effective interventions for control and prevention. A lack of immunological information is due to the recent discovery. Preliminary studies suggest that SARS-CoV-2 is quite similar to SARS-CoV based on the full-length genome phylogenetic analysis[18,19]and the putatively similar cell entry mechanism and human cell receptor usage[20].Due to this apparent similarity between the two viruses, documented data has provided an understanding of protective immune responses against SARSCoVand may aid in vaccine development[21.]

Various reports related to SARS-CoV suggest a protective role of both humoral and cell-mediated immune responses. For the former case, antibody responses generated against the S protein, have been shown to protect from infection in mouse models. In addition, multiple studies have shown that antibodies generated against the N protein of SARS-CoVwere particularly prevalent in SARS-CoV-infected patients. While being effective, the antibody response was found to be short-lived in convalescent SARS-CoV patients[22.].

In contrast, T cell responses have been shown to provide long-term protection even up to 11 years postinfection[23], and thus have also attracted interest for a prospective vaccine against SARS-CoV[24]. Among all SARS-CoV proteins, T cell responses against the structural proteins have been found to be the most immunogenic in peripheral blood mononuclear cells of convalescent SARS-CoV patients as compared to the non-structural proteins. Further, of the structural proteins, T cell responses against the S and N proteins have been reported to be the most dominant and long-lasting[25].

The identification of SARS-CoV-derived epitopes that map identically to SARS-CoV-2promotes further research in exploring vaccines designed to induce a protective T cell response, which has been shown to provide long term protection in SARS-CoV. Linear SARS-CoV-derived B cell epitopes in the S2 subunit may potentially be more promising candidates for inducing a protective antibody response. Numerous of these epitopes, while being less exposed, are found to map identically to SARS-CoV and SARS-CoV-2, and preliminary results suggest their role in generating cross-reactive and neutralizing antibodies. Hence, vaccine solutions that attempt to induce antibodies that target the S2 linear epitopes may be effective and should be inquired.

A preliminary analysis of linear SARS-CoV-derived B cell epitopes has been reported online on the ViPR database website.Itconsideredlinear B cell epitope data for all Betacoronaviruses from human hosts.

Mutations can take place as the virus continues to evolve which stress the need forfurther studies (T cell and B cell assays) to determine the potential of the identified epitopes to induce a positive immune response against SARS-CoV-2. This would help to further refine the reported epitope set, based on observed immunogenicity; an important consideration for immunogen design. Overall, as the identified set of SARS-CoV epitopes map identically to SARS-CoV-2, they present potentially useful candidates for guiding experimental efforts towards developing vaccines against SARS-CoV-2.

Unfortunately, creating a vaccine capable of preventing the coronavirus that causes COVID-19 will probably take at least a year to 18 months, health officials say. While there are about 10 vaccine candidates in the works and at least could begin clinical trials in April it would still take about three more months to conduct the first stage of human testing and another eight months or so to complete the next stage of the trial process. New vaccines require extensive study and time-consuming tests that can result in financial constraints. There‘s no guarantee of success, but even if everything goes well, the final product might not hit the market until after an outbreak has subsided. *Concept of vaccine*

Our body has a defence system to identify and encounter foreign objects. There are numerous types of white blood cells:

- Macrophages engulf pathogens or cells that are dead or damaged. They leave behind identifying fragments of the invading microbes called antigens.
- B-lymphocytes produce antibodies that recognize and bind to those antigens. If a pathogen with those antigens shows up in the blood stream again, those antibodies can mount an attack.
- T-lymphocytes can attack the infected cells.

A vaccine provides a memory response. It helps immune system learn to recognize a specific threat by creating an illusion of attack so that antibodies are produced without a real infection.

Types of vaccines:

- Attenuated - live microbe weakened in order to avoid serious disease in a healthy immune system. (chickenpox, measles).
- Inactivated - killed microbes. May require boosters over time. (polio).
- Toxoid - weakened versions of the toxins released by invading bacteria. (diphtheria, tetanus). Subunit - fragments of microbe. (Pertussis)
- Conjugate –microbes that disguise antigens.

Development of vaccines

The immune system learns to counteract a virus based on the surface antigens. So a vaccine should present an image of the organism. Vaccines can be developed by:

Injecting a person with a killed virus or live viruses that have been grown and weakened intentionally, typically by removing specific genes in their RNA or DNA.Both of these strategies take some time, and scientists worry that if they use them on novel viruses, they may not behave the way researchers predict, said Dr.Kathryn Stephenson, who runs the clinical trial unit at Beth Israel Deaconess Medical Centre for Virology and Vaccine Research.

Creation of antigen from viral genetic code, which may be made of either RNA or DNA.Nowadays, researchers can get started fast. Scientists in China made the coronavirus‘ RNA sequences available on Jan. 10, and many labs began working toward a vaccine the next day, Stephenson said.

There are many different vaccine-making platforms, each with its own set of advantages and disadvantages.A vaccine based on the virus‘ genome can be made quickly but it may be harder to manufacture in surplus amounts.Another option is to take the viral antigen and put it into a viral vector vaccine that enters cells, prompting them to produce huge numbers of this antigen for an immune response. These vaccines take longer but they can be scaled up more readily.

Safety and manufacture of vaccines

Before a vaccine candidate is approved for use, it must be proven safe and effective in a series of trials that are monitored by the Food and Drug Administration.

The first step is to show that it‘s safe in preclinical studies. These can be conducted in vitro (using cells in a laboratory dish) or in vivo (using an animal as a stand-in for humans). The new virus shares much of its genome with the coronavirus that caused the 2003 outbreak of severe acute respiratory syndrome, and some Australian researchers already have been studying the SARS virus in ferrets.

Then clinical trials in humans can begin. Phase 1 trials are small, usually with a few dozen closely monitored participants. The main goal here is to make sure the vaccine is safe. Phase 2 trials typically enroll hundreds of patients to expand the safety assessment and allow scientists to dig into the body‘s immune response. Phase 3 trials can enroll thousands of people, typically with some of them randomly assigned to get the vaccine and some getting a placebo.

This process can take years under normal circumstances. In an emergency, it could be sped up dramatically. The big sticking point is often the Phase 3 trial. In an epidemic, many study volunteers may not want to risk getting a placebo instead of the vaccine. Researchers employed a novel experimental design during the Western African Ebola outbreak, 2014, that involved vaccinating people with varying degrees of separation from an Ebola patient and using computer models to help determine if the vaccine had had an effect.

It has to protect enough people with few unwanted side effects. Qualification of safety may depend on the disease in question.

A cooperative and passionate manufacturerfor the laboratories is the cream of any vaccine development. And many companies debate over the investmentfor a new vaccine as there is possibility that the epidemic could end before there‘s a chance to bring it to market. Quality is a serious technical challenge in large-scale manufacturing.Every vaccine has an identity.The manufacturing challenges mainly involve safety precautions and contents post-manufacture.

Availability of vaccines

The main challenge is about the distribution of vaccines when the demand exceeds the supply.Vaccines are often less effective in older people than they are in younger ones, and this could affect the way that a vaccine is administered. Since older adults appear to be most at risk from COVID-19, it‘s likely that health officials would focus on them first. But the controversy is that the younger generation needs to be protected as they are the stepping stones of the future. Medical professionalsat high risk of exposure and needto care for the affected should be a

priority.Front-line healthcare workers are usually one of the first groups to vaccinate as they form the workforce.A booster dosage maybe given, if indicated.

The urgent need of vaccine has put a lot of pressure on scientists. It is still uncertain about the immune reactions of the body against the virus and how safe a vaccine is to initiate a similar response. To some extent, it is possible to analyse this from already infected patients and animal studies. There is a debate regarding the safety trials to be done in human beings without adequate data on the immune reactions. On the other hand, if the vaccines developed in a fast pace prove to be ineffective or harmful to the individuals, it can lead to further complexities in the trials and thereby leading to further delay in availability of an effective and safe vaccine. A vaccinated healthy individual develops an immune response without having to face the real infection. The coronaviruses that cause common colds provide short-term immunity suggesting the probability of encountering a reinfection despite having high antibody levels.

The phase I trial focuses on the safety of a vaccine developed by Moderna, a company based in Cambridge, Massachusetts[26]. But researchers will also look closely at the nature of the immune response the vaccine summons. The Moderna vaccine consists of an RNA molecule. It is designed to train the immune system to make antibodies that recognize and block the spike protein that the virus uses to enter human cells.A successful SARS-CoV-2 vaccine might need to prompt the body to generate antibodies that block other viral proteins or make T cells that can recognize and kill infected cells.

Vaccines are a necessity for reducing and ultimately eradicating SARS-CoV-2. Inactivated vaccines are one major type of conventional vaccines that could be easily produced and quickly developed. In this approach, SARS-CoV-2 virions can be chemically and/or physically inactivated to elicit neutralizing antibodies. While inactivated vaccines should still be tested, alternative approaches include live attenuated vaccines, subunit vaccines and vectored vaccines. All of these need to be analysed by further studies and tests in animals.

As they are given to large numbers of healthy people, vaccines normally have a higher bar for safety than therapeutic drugs administered for the diseased. A phenomenon called disease enhancement should be ruled out, in which vaccinated people get infected, develop a more severe form of the disease than people who have never been vaccinated. At the moment, scientific research is growing to develop a coronavirus vaccine. In recent days, China has announced the first animal tests, and researchers from the University of Queensland in Australia have also announced that, after completing the three-week in vitro study, they are moving on to animal testing. Furthermore, in the U.S., the National Institute for Allergy and Infectious Diseases (NIAID) has announced that a phase 1 trial has begun for a novel coronavirus immunization in Washington State.

As vaccine development is a very complicated and long process even after massive hardship it takes atleast few months for effective vaccine to come in to market.

Is it mutated?

The coronavirus is rapidly spreading around the world. Researchers say the virus is changing its genetic makeup slightly. It‘s normal for viruses to undergo evolution when they are transmitted to a new host. Does the virus have mutated forms? Is the virus getting more pathogenic? Can this hinder the production of vaccines? Coronaviruses like all viruses change small parts of their genetic code all the time.Like flu and measles, the coronavirus is an RNA virus. During a viral infection, the virus enters a cell and replicates causing spread of infection which is dependent on its genetic constitution. The altered virus duplicates to other cells in the body.

So far, researchers who are tracking the genetic changes in SARS-CoV-2 say it seems relatively stable.Researchers are on alert for changes that might affect how the coronavirus behaves in humans. For instance, if the coronavirus developed ways to block parts of our immune system, it could hide out in our bodies and establish itself better. If it evolved to bind more strongly to human cells, it could enter them more efficiently and replicate more quickly..

Two strains of the new coronavirus are spreading around the world, according to an analysis of 103 cases. But the World Health Organization insists that there is no evidence that the virus has been changing. Viruses are always mutating.When a person is infected with the coronavirus, it replicates in their respiratory tract. Every time it does, around half a dozen genetic mutations occur, says Ian Jones at the University of Reading, UK.

When Xiaolu Tang at Peking University in Beijing and colleagues studied the viral genome taken from 103 cases, they found common mutations at two locations on the genome. The team identified two types of the virus based on differences in the genome at these two regions: 72 were considered to be the ―L-type‖ and 29 were classed ―S-type‖[27].

A separate analysis by the team suggests that the L-type was derived from the older S-type. The first strain is likely to have emerged around the time the virus jumped from animals to humans. The second emerged soon after that, says the team. Both are involved in the current global outbreak. The fact that the L-type is more prevalent suggests that it is more aggressive than the S-type.It is vital to know how many strains of the virus exist.

The differences between the two identified strains are tiny. In fact, they can't really be considered to be separate strains. And many of the genetic differences won't affect the production of proteins, and so won't change the way the virus works, or the symptoms it causes.

In all practical terms, the virus is as it was when it originally emerged. There's no evidence it is getting any worse. The sentiment is echoed by the World Health Organization. But we can't say for sure. The study only represents 103 cases. We can expect more strains to emerge. This is the case with seasonal flu, new variants crop up every year that can infect people whether or not they've had flu in the past.

"Viruses mutate naturally as part of their life cycle," says Ewan Harrison, scientific project manager for the COVID-19 Genomics UK Consortium, a new project that tracks the virus in the United Kingdom.Inevitably, viruses "make mistakes in their genomes" as they copy themselves. Those changes can accumulate and carry over to future copies of the virus. Researchers are using these small, cumulative changes to trace the pathway of the virus through groups of people. It acquires about two mutations a month during this process of spread.

Coronaviruses differ from flu viruses in another key way that reduces the number of mutations. They proofread their own genomes when they copy themselves, cutting out things that don't seem right. They maintain this ability to keep their genome pretty much intact.

Nonetheless, their relatively larger size means more capability of fighting off a host's immune system and making copies of themselves. But it's not as if the coronavirus needs to become more potent to survive and thrive. It's already replicating itself around the world very successfully.

Selective pressures could come from introducing treatments and vaccines that are effective against a narrow group of coronavirus strains. If that happens, strains that aren't targeted by these measures would likely proliferate.

Projects such as the COVID-19 Genomics UK Consortium will use these genetic drifts to track the path of the virus and figure out if there are hospitals or community hubs that are hot spots for contagion, according to Harrison. This will give public health officials a sense of where and how the virus is being transmitted now.

Will the coronavirus surge when schools reopen? Will new strains emerge that develop resistance to drugs or vaccines that are introduced? To answer such questions, the long-term plan is to track the virus in real time and see how it changes as it spreads.

Latest coronavirus research by a team of researchers from Nankai University in Tianjin lead by Professor RuanJishou, a prominent virologists and genomicist have discovered that the new SARS-Cov-2 coronavirus that causes the Covid-19 disease has a mutated gene that is found in HIV virus. It is this unique feature that sets it aside from the rest of the known coronaviruses.

These findings have huge implications on the potency of the coronavirus and also what it can cause in humans, not just the Covid-19 disease. Furthermore, the Covid-19 disease should never be compared to like the common cold or influenza virus as this new coronavirus is in a separate league of its own. Because of the HIV-like mutations, its ability to bind with human cells could be as much as 1,000 times more potent that the initial SARS virus of 2003.

The findings also indicate that the new SARS-CoV-2 has a ‗dual attack' approach of binding to human cells. The first is via the ACE2 receptors found on human cell membranes and it's a typical mode of most coronaviruses. However it must be noted that the ACE2 protein does not occur in large quantities in healthy people, and this partly helped to limit the scale of the SARS outbreak of 2002/2003 which infected close to 8,000 people globally.

As the findings of the new study indicates that the new SARS-CoV-2 coronavirus has a mutated gene similarly found on the HIV virus, it is also able to attack human cells via the target called furin, which is an enzyme that works as a protein activator in the human body. Typically many proteins are inactive or dormant when they are produced and have to be cut at specific points to activate their various functions which furin does in the human cellular pathways. This finding suggests that 2019-nCoV coronavirus may be significantly different from the SARS coronavirus in the infection pathway and has the added potency of using the packing mechanisms of other viruses such as HIV.

Mutation can generate a structure known as a cleavage site in the new coronavirus' spike protein.Typically, a virus uses the outreaching spike protein to hook on to the host cell, but normally this protein is inactive. The cleavage site structure's role is to trick the human furin protein, so it will cut and activate the spike protein and cause a ―direct fusion‖ of the viral and cellular membranes.

The new findings is bringing scientists and researchers towards understanding how the new coronavirus behaves and how it makes us ill plus helps in developing treatment protocols. Experts' perception of the new coronavirus has changed dramatically over the past few weeks. The link to the furin enzyme could shed light on the coronavirus' evolutionary history before it made the jump to humans. The mutation could come from many possible sources such as a coronavirus found in rats or even a species of avian flu.

However no major mutations have taken place as in the case of most typical coronaviruses when they replicate and lead to their inefficiency and eventual demise as in the case of the original SARS, these new coronavirus is extremely stable in transmissions and replications and is in fact becoming more virulent, indicating we are dealing with a strain that is going to be with us for a longtime.

It is also important for all experts to note that the coronavirus has a 96 percent match to the BatCoVRaTG13 coronavirus versus an approximate 82 per cent match to the original SARS coronavirus. Shifting a focus from the original SARS coronavirus which many experts tend to focus on when making doing studies and comparisons to instead the Bat-CoVRaTG13 coronavirus might also reveal more details about the new SARSCoV2 as these bat viruses have evolved over time and possess many unique properties that we have yet to understand.

Will it reinfect?

Is it a possible scenario that once a person infected with the coronavirus is unlikely to have the disease again,provided there is no mutation of the virus? Most researchers assume that people who have recovered from SARS-CoV-2 infection will develop immunity and remain protected. But that assumption needs to be proved.

The number of global cases of the new coronavirus has reached more than 20,55,943, as the pandemic continues its spread around the world. However, the latest figures also show more than 89,000 people, many of whom are in China where the virus originated, have recovered from the disease.While the recovery rate is promising, it does not mean that those who have been infected with coronavirus are not still at risk, as experts believe having the virus once does not mean you cannot get sick from it again.

According to Li QinGyuan, director of pneumonia prevention and treatment at China Japan Friendship Hospital in Beijing, those who have been infected with Covid-19 develop a protective antibody - but it isn‘t clear how long the protection lasts.

However, in certain individuals, the antibody cannot last that long. For many patients who have been cured, there is a likelihood of relapse. In children, it is currently believed that the virus causes the development of short-term immunity.

Coronaviruses have been to existence for a long span invading many species. It is probable that an infection results in immunity in most individuals as is seen with other coronaviruses. This puts forward the concept of relapse of the disease rather than a reinfection.

People with mild infections can test positive for the virus by throat swabs for days and even weeks after their illness. But, that doesn‘t mean it isn‘t possible to contract the disease again, especially in those who are immunocompromised.

While further studies are needed to understand whether it is possible for an individual to be reinfected with new coronavirus, experts recommend those who have been infected follow the hygiene steps outlined by CDC, which include staying away from people who are sick, frequently washing hands, and covering coughs and sneezes.

Now, a collaboration of Chinese scientists has dug deeper into whether or not reinfection with SARSCoV2 is possible with a small monkey study. The team looked at whether or not non-human primates, rhesus macaques, can become reinfected with SARS-CoV-2. The work was posted on the preprint server *bioRxiv* on March 14 in a paper titled, ―Reinfection could not occur in SARS-CoV-2 infected rhesus macaques[28].‖ Their conclusion: there may be no reason to worry about reinfection.

The fact that little is known about this new virus is very alarming, as the possible reinfections and latent viral loads in the body that may cause short term, midterm or long term effects remain unveiled.As of the available resources there is a high chance of reinfection specially in immunocompromised people.

Human convalescent serum is an option for prevention and treatment of COVID-19 disease that could be rapidly available when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum.

Does Passive antibody therapy has any role?

Passive antibody therapy involves the administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent[29]. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Thus, passive antibody administration is the only means of providing immediate immunity to susceptible persons.

In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibodydependent cellular cytotoxicity and/or phagocytosis. Possible sources of antibody for SARS-CoV-2 are human convalescent sera from individuals who have recovered from COVID-19 or preparations generated in certain animal hosts, such as genetically engineered cows that produce human antibody. Although many types of

preparations are or will soon be under development, the only antibody type that is currently available for immediate use is that found in human convalescent sera. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase.

An individual who is sick with COVID-19 and recovers has blood drawn and screened for virusneutralizing antibodies. Following identification of those with high titres of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in the treatment of established disease.

A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease. Another explanation is that antibody works by modifying the inflammatory response, which is also more easily achieved during the initial immune response, a stage that may be asymptomatic.

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues, and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to month.

These procedures serve as notable milestones for the successful development of a vaccine.There are reports that convalescent serum was used for therapy of patients with COVID-19 in China during the current outbreak. Although few details are available from the epidemic in China and published studies involved small numbers of patients, the available information suggests that convalescent serum administration reduced viral load and was safe.

COVID-19 convalescent sera can be used for either prophylaxis of infection or treatment of disease. In a prophylactic mode, the benefit of convalescent serum administration is that it can prevent infection and subsequent disease in those who are at high risk for disease, such as vulnerable individuals with underlying medical conditions, health care providers, and those with exposure to confirmed cases of COVID-19 The efficacy of these approaches cannot be inferred without carrying out a controlled clinical trial. Based on the historical experience with antibody administration, it can be anticipated that antibody administration would be more effective in preventing disease than in the treatment of established disease.

Every procedure involves a certain amount of benefits and risks. Known risks are those associated with transfer of blood substances. With modern blood banking techniques that screen for blood-borne pathogens and match the blood type of donors and recipients, the risks of inadvertently transferring known infectious agents or triggering transfusion reactions are low.

Theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may prevent disease in a manner that attenuates the immune response, leaving such individuals vulnerable to subsequent reinfection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity. This concern could be investigated as part of a clinical trial by measuring immune responses in those exposed and treated with convalescent sera to prevent disease. If the risk proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

Given that historical and current anecdotal data on use of convalescent serum suggest it is safe in coronavirus infection, the high mortality of COVID-19, particularly in elderly and vulnerable persons, suggests that the benefits of its use in those at high risk for or with early disease outweigh the risks. However, for all cases where convalescent serum administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

We anticipate that once the necessary regulatory permissions are in place, individuals who recover from COVID-19 can be approached to donate blood for serum preparation or antibody isolation through apheresis.
Recovery from COVID-19 will be assessed clinically, and such individuals must be shown to free of SARS-CoV2, including in their blood by appropriate viral nucleic acid screening. Donated blood products will be screened for infectious agents according to current blood banking practices, and individual sera will be studied for specific antibody content and neutralizing activity to SARS-CoV-2. Depending on the volumes needed and the neutralizing activity of donated convalescent sera, these could be pooled or used individually, and preparations for clinical use would be treated for pathogen attenuation. At this time, we do not know what an effective neutralizing titer would be in a susceptible individual given passive antibody therapy for prophylaxis, and determining this parameter would be part of the study design. Similarly, we do not know what doses would be effective therapeutically.

Passive antibody therapy is a promising therapy in the reduction and control of the disease at present. This can be applied for prevention in exposed individuals and in early stages of the disease. It is anticipated that convalescent serum will prevent SARS-CoV-2 infection in those to whom it is administered. The most vulnerable category is the health workers who are being quarantined in suspected cases. This allows many hospitals to continue their first line defence without the fear of the employees getting infected and promotes the smooth running of the system. Another reassurance is for the family members who are taking care of an infected patient at home. As time tightens the grip amidst the harsh reality of the pandemic, emergency prophylactic management is the satisfying solution.

II. Conclusion

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global health emergency. The epicenter of this ongoing outbreak is in the city of Wuhan in Hubei Province of central China and the Huanan seafood wholesale market was thought to be at least one of the places where SARS-CoV-2 from an unknown animal source might have crossed the species barrier to infect humans.

World Health Organisation is rapidly undertaking all possible measures to control the disease. Many nations are facing huge crisis in terms of finance, available resources and sufficient number of health workers.It was found that covid 19 virus developed as a natural selection process and there is no strong evidence for laboratory generation till now. Mutated forms present a challenge to the development of vaccines. Much insight is required concerning the viral reactions, transmission pathways, alternate forms, immune responses and management of the epidemic. There is high pressure on scientists around the globe for effective therapeutic strategies and development of safe vaccines. Time is of essence. The probability of reinfection should not be ruled out even if the patient presents a short term immunity. Treatment protocols should focus on recovery in diseased patients, prevention of spread of infection, vaccination and ultimately complete eradication of the virus. At the moment, passive antibody therapy paves way to a hopeful future. It is important to create awareness among the general population and not to panic. Redoubling our research efforts on SARS-CoV-2 and COVID-19 will solidify the scientific basis on which important decisions are made.

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