

A Comprehensive Review on COVID-19 Evolution and Development

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Abstract

The emerging pandemic causing flu-like symptoms in patients is caused by the novel Coronavirus that was previously called 2019-nCoV. The mutated gene of SARS-CoV was transformed to SARS-CoV-2 in animals and further transmitted to humans in the month of December 2019 in Wuhan city of China. Eventually, the novel coronavirus spread all around the globe as a highly contagious disease. COVID-19 (the illness caused by coronavirus) has affected 213 countries and territories around the world. There are about 18,852,205 new positive cases, 707,451 casualties, 12,032,508 recoveries till date that is, 05th August 2020. This virus resulted in Acute Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction. Human transmissions are caused due to inhaling or by contact with viral droplets. The infected patient seems to show an incubation period of 2–14 days. Due to this ominous situation, several countries got shut down to contain the spread of novel coronavirus. This review article includes the etiology, epidemiology, detection and diagnosis, histopathology, pathophysiology of novel coronavirus. To control the virus, many drugs are in use. Short-term testing kits have been discovered by many countries using the Reverse transcriptase-polymerase chain reaction (RT-PCR) technique. Vaccines from numerous research laboratories are at the stage of human trials. This review article can be preferred for further investigation on coronavirus.

Keywords: Acute respiratory distress syndrome (ARDS), COVID-19, etiology, epidemiology, SARS-CoV, SARS-CoV-2, novel Coronavirus, reverse transcriptase-polymerase chain reaction (RT-PCR)

INTRODUCTION

Coronavirus outbreak is the major outbreak that emerged on December 8th, 2019 from the Wuhan city of China, and it was rapidly spread among the people. The infected people in China also infected the people of other countries. Most of the first group of patients infected this time were customers or workers at a local seafood wholesale market in Wuhan, China [1]. The first image of Novel coronavirus isolated from the samples of the patients is given in Figure 1. The size of the virus was seen to be about 0.06 to 0.14 microns, containing single-stranded RNA as its genetic sequence. The

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major medium of transmission of coronavirus is through air. The virus primarily infects the gastrointestinal tract and upper and lower respiratory tract of birds and mammals. Most of the coronavirus causes only mild flu-like symptoms, MERS-CoV (Middle East Respiratory Syndrome Coronavirus), and SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) induce severe respiratory illness. This occurred due to zoonotic transmission [2]. This is the condition where the viral transmission is caused directly from animals. The previous SARS and MERS of the animal viruses underwent a series of genetic mutations that made them capable of infecting humans and resulted in spreading from one individual to

another. Studies have shown that the source of MERS-CoV and SARS-CoV were bats and animals such as camels, bats, and snakes. Snakes served as intermediate hosts between bats and humans, respectively.

THEORIES OF EMERGENCE

Scientists and researchers believe that this novel coronavirus might have evolved from bats and entered into human population via an intermediate animal host [3].

First Theory

The new virus may have evolved in an animal then it became pathogenic (causing-illness) before it jumped to humans; this is how we get SARS from civet cats and MERS from camels. In the case of new coronavirus, the animal may have been a bat that transmitted the virus to another intermediate animal that finally brought the novel coronavirus to humans [4].

Second Theory

The new virus doesn't cause any illness in animals but once it jumped into humans, it evolved into a disease-causing strain there. The spike proteins of some coronavirus from pangolins have similar Receptor-Binding Domain (RBD) structure to that of the novel coronavirus. If the second theory is true, then the novel coronavirus may have originated in pangolins [5].

Figure 1 depicts the physical appearance of the novel coronavirus and (a), (b) and (c) represent the transmission electron microscopic images from the Center for Disease Control and Prevention (CDC) showing the SARS-CoV-2 coronavirus in the samples taken from the first American patient affected with COVID-19. Here the virus particles are colored artificially in blue which are used to identify the type of pathogen. This is the conventional way to diagnosing patients with contagious diseases.

NAMING OF CORONAVIRUS DISEASE (COVID-19)

Generally, names of the viruses are assigned by the International Committee on Taxonomy of Viruses (ICTV). Various processes and purposes are involved in naming viruses and their attributed disease. The most important concern for naming is the genetic structure of the virus, which facilitates the virologists and other scientific communities for the development of diagnosis kits and vaccines.

On 11th February 2020, ICTV gave the name to the novel coronavirus as "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" based upon the genetic similarities to the coronavirus that is accountable for the SARS epidemic in 2003 [6].

Chan *et al.* [1] has proved that the new virus is termed as SARS-CoV-2 after identifying its similarities of about 82% with the genomic sequence of Human SARS-CoV and 89% with the genomic sequence of Bat SARS-like-CoVZXC21, which is also similar to genome of new HCoV isolated from sample clusters of typical pneumonia patient who returned after his visit from Wuhan, China.

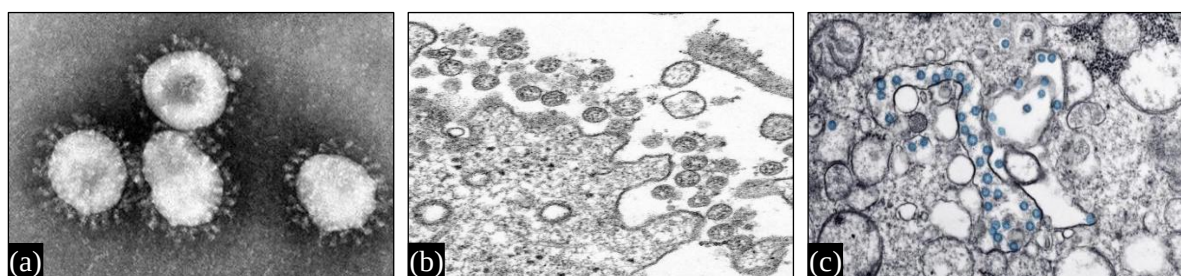


Figure 1. Images released by the Centre of Disease Control (CDC) and World Health Organization (WHO). (a) Image of Lab Grown Novel Coronavirus (b) Image of Coronavirus from the Sputum Sample of the Affected Patient and (c) Image Depicting the Virus Particles in Blue Color in the Sample of Affected Patient.

ETIOLOGY/CLASSIFICATION

Order: Nidovirales

Family: Coronaviridae

Subfamily: Orthocoronavirinae

The term “Coronavirus” is taken from the Latin word “coronum” which meaning “crown” or “halo”. This referred to the attributes such as crown-like appearance or a solar corona around the virions (virus particles) when observed under two-dimensional transmission microscope; this is because the surface is covered with a club-shaped protein spike [7]. The Subfamily *Orthocoronavirinae* belonging to Family *Coronaviridae* that is under the Order *Nidovirales* subdivides the coronavirus into four different genera: α CoVs (Alpha Coronavirus), β CoVs (Beta Coronavirus), γ CoVs (Gamma Coronavirus), δ CoVs (Delta Coronavirus). According to Cascella *et al.* [3], the SARS-CoV-2 is in the form of β CoVs that are elliptical or round in shape. It is sensitive to ultraviolet rays and heat like that of other CoVs. Due to the bilipid layered membrane, the inactivation of these microorganisms can be effectively done by lipid solvents such as ethanol, petroleum ether, and chlorine-based disinfectant such as sodium hypochlorite, peroxyacetic acid and chloroform. Coronavirus contains the +ve single stranded RNA genome which is enveloped within a nucleocapsid of helical symmetry. When it enters into the host cell, the coat of the virus particle is denuded and RNA genome enters into the cytoplasm of the cell. Using host cell machinery, the protein “Replicase” which is encoded by the viral genome allows to transcribe into new RNA copy.

SARS-CoV-2 is surrounded by bilipid layer as an envelope. On the surface, there is Spike (S) protein (PDB code–6CRV), Membrane (M) protein (PDB code–5X29), HE-protein, Envelope (E) protein (PDB code–3I6G) and Nucleocapsid protein (N) [8].

PATHOPHYSIOLOGY

China was the first country to decode the genome of the novel coronavirus (2019-nCoV). This is a positive single-stranded RNA virus with nucleocapsid. The genome structure is of approximately 30kb in length which is largest among the known RNA viruses with a 5'-cap and 3'-poly-A tail structure [1–9]. The genome of SARS-CoV-2 is composed of 29,891 nucleotides, encoding for 9860 amino acids and its diameter is about 80–120 nm. The G + C content were 38%. The 2019-nCoV (human) genome comprises of two flanking untranslated regions (UTRs) on either side of the single long operon reading frame. This encodes a polyprotein similar to other β CoVs. The arrangement of genome is in the order of 5'-replicase (orf1/ab)-structural proteins [spike (S)-Envelope (E)-Membrane (M)-Nucleocapsid (N)]-3' further lacking the *Hemagglutinin-Esterase* gene [1–3]. The genome of 2019-nCoV is represented in Figure 2 [1].

The transcription is carried over through the Replication–Transcription Complex (RCT) arranged in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Twelve putative, functional open reading frames (orfs) shown in Figure 2 (a) are expressed from a nested set of nine subgenomic mRNAs carrying a conserved leader sequence in genome, nine transcription-regulatory sequences, and two terminal UTRs. As shown in Figure 2 (b and c), 5'-UTR and 3'-UTR are made up of 265 and 358 nucleotides, respectively [1]. From the beginning of the sequence, there are pp1a and pp1ab polyproteins at the 5'-terminal which are responsible for the enzyme replicase where these are encoded in orf1a/b. Also orf1a/b is proteolytically cleaved into 16 putative non-structural proteins (Nsps) which cover around 2/3rd of orf1a/b. These sixteen Nsps are responsible for replication of the genome which carries many enzymes such as two viral cysteine proteases, namely Nsp3 (papain-like protease) and Nsp5 (chymotrypsin-like protease which acts as a 3CLpro domain or Mpro) [10]. Nsp12 is responsible for RNA-dependent RNA polymerase production and Nsp13 is responsible for helicase. Nsp1 is responsible for suppressing the antiviral host response. The 16 putative Nsps and their functions are listed in the Table 1.

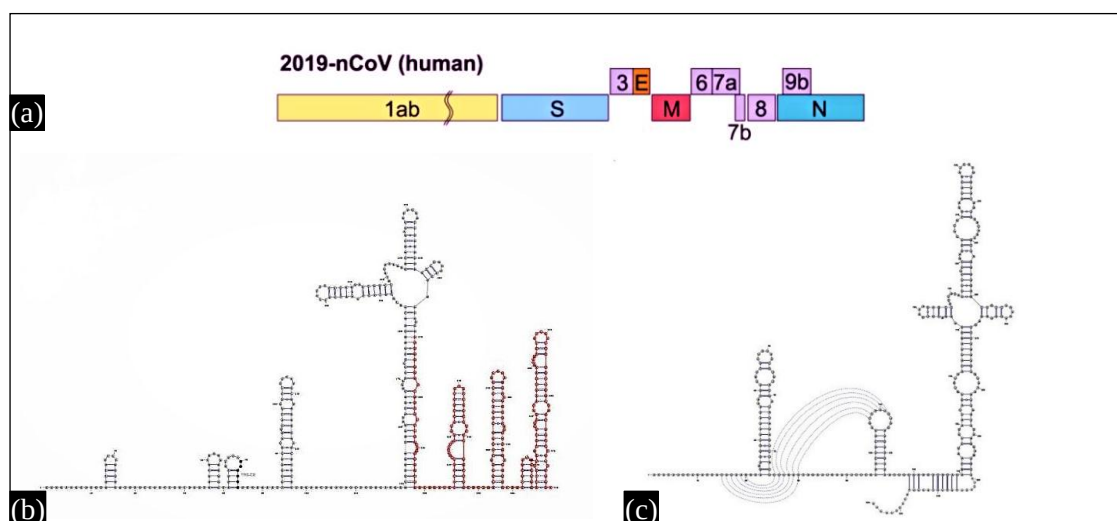


Figure 2. Genome Organization of COVID-19 with 5'-UTR (Untranslated region), Open Reading Frame (orf), and 3'-UTR. (a) Open Reading Frame here the Beta coronavirus genome comprises 1a/b (yellow box), encoding non-structural proteins (Nsp) for replication, structural proteins including spikes (blue box), envelope (orange box), membrane (red box), and nucleocapsid (cyan box) proteins, accessory proteins (purple box) (b) 5'-UTR and (c) 3'-UTR

Table 1. 16 Putative Proteins and their Functions.

NSP	Putative function/domain
Non-structural protein 1	Suppress antiviral host response
Non-structural protein 2	Not known
Non-structural protein 3	Putative PL-pro domain
Non-structural protein 4	Nsp3 and 6 complexes: Formation of DMV
Non-structural protein 5	3-CLpro domain
Non-structural protein 6	Nsp3 and 4 complexes: Formation of DMV
Non-structural protein 7	Complex with Nsp8: Primase
Non-structural protein 8	Complex with Nsp7: Primase
Non-structural protein 9	RNA/DNA binding
Non-structural protein 10	Complex with Nsp14: Replication fidelity
Non-structural protein 11	Short peptide at the end of orf1a.
Non-structural protein 12	RNA-dependent RNA polymerase
Non-structural protein 13	Responsible for Helicase enzyme
Non-structural protein 14	Exon: 3'-5' Exonuclease.
Non-structural protein 15	Xendo U: Poly(U)-specific endoribonuclease
Non-structural protein 16	2'-O-ribose methyltransferase.

Spike proteins contain S1 and S2 subunits of glycoproteins. There are homotrimers like the N-terminal domain (NTD) and receptor-binding domain (RBD) with a single peptide in the S1 subunit. Whereas in the S2 subunit it is composed of conserved Fusion peptide (FP), Heptad repeat (HR)1 and 2, Transmembrane domain (TM) and a Cytoplasmic domain (CD). These all lead the spike protein of the viral particle to attach to the host cell receptors. According to the researchers, these proteins bind to the Angiotensin-Converting Enzyme 2 (ACE2) receptors present on the exterior of the lungs to gain entry into them and it also binds to the cells of the gastrointestinal tract.

EPIDEMIOLOGY

SARS-CoV-2 Outbreak

Around the globe, 213 countries and territories have claimed a total of 18,852,205 confirmed cases of COVID-19 (until 2020 August 5). Of these, 99% are in mild condition and 1% are in serious or

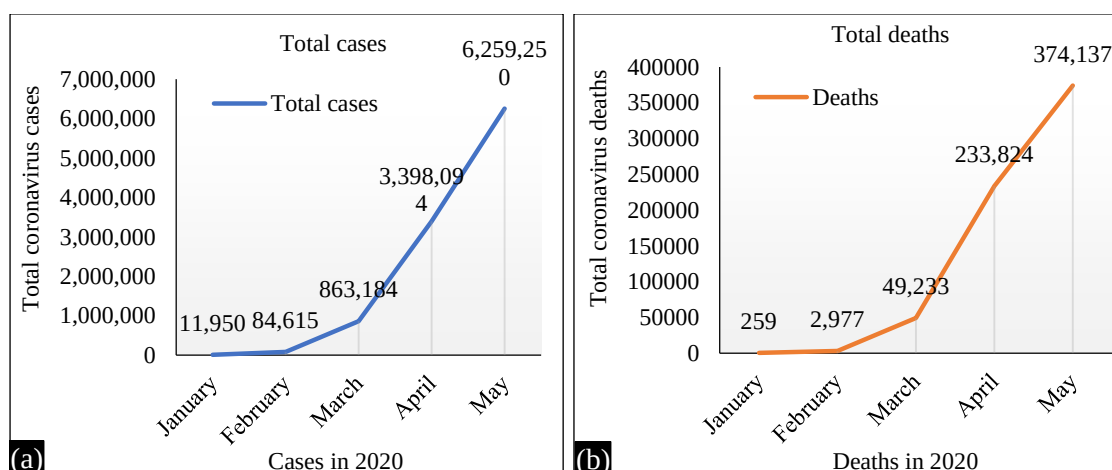


Figure 3. Data from Worldometer Website till 2020 June 3. (a) Total cases registered and (b) Total deaths confirmed

Table 2. List of Top 10 Countries got Affected by COVID-19.

Country	Cases	Deaths
United States	4,947,715	161,088
Brazil	2,817,473	96,326
India	1,963,239	40,739
Russia	866,627	14,490
South Africa	521,318	8,884
Mexico	449,961	48,869
Peru	439,890	20,007
Chile	364,723	9,792
Spain	352,847	28,499
Columbia	334,979	11,315

critical condition. A total of 707,451 deaths have been recorded. The number of recoveries stands at 12,032,508 [11]. Total cases and deaths are represented in Figure 3.

As per total reports, top 10 countries that were affected with COVID-19 are listed in Table 2.

HISTOPATHOLOGY

According to the histopathological data [12], doctors identified some traces of infection when two COVID-19 patients underwent lung lobectomies for adenocarcinoma. Pulmonary CT scan of two patients resulted in edema and important proteinaceous exudates as large protein globules. Vascular congestion along with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes has been reported [3] in addition to acute respiratory distress syndrome (ARDS).

Mild Condition: In 80% of cases, patients reported either non-pneumonia or mild pneumonia condition.

Severe Condition: In 14% of cases, patients reported respiratory frequency $\geq 30/\text{min}$, dyspnea blood oxygen saturation (spO_2) $\leq 93\%$, $\text{PaO}_2/\text{FiO}_2$ ratio or P/F [the ratio between the vital sign of the oxygen (partial pressure of the oxygen, PaO_2) and therefore the percentage of oxygen supplied (fraction of inspired oxygen, FiO_2)] < 300 , and/or lung infiltrates $> 50\%$ within 24–48 h.

Critical Condition: In 5% of cases, patients reported respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or multiple organ failure (MOF) [2, 3].

DETECTION AND DIAGNOSIS

Physical Examination

It is more likely to cause chronic disease among elderly, who have much mortality rate if they contract it. Common symptoms of SARS-CoV-2 usually begin in 2–15 days after contracting with the virus [12, 13]. The symptoms are fever, ARDS [14], fatigue and dry cough. Other symptoms include sputum formation, breathlessness, sore throat, headache, myalgia (muscle pain) or arthralgia (joint pain), chills, nausea and nasal congestion. Less frequent symptoms include diarrhea, hemoptysis (coughing up blood from the respiratory tract) and conjunctival congestion. Majority of the symptoms are generally mild, and about 80% of individuals who gets affected with the virus often recover without any special treatment. Although, one in seven patients become critically ill and develop breathing difficulties.

Experts suspect a new symptom of the novel coronavirus. Red or purple lesions on the hands and toes of the patients have been detected by the Dermatologists of Italy in March 2020. These are named as "COVID toes". The American Academy of Dermatology has compiled a registry of skin manifestations related to COVID-19. There are about more than 300 total cases on the dermatology registry consisting of COVID toes.

Viral conjunctivitis is also observed in some patients as traces of viral particles are found in the eye discharge of the coronavirus patient. This shows that the tears of the patient are also contagious [15].

Detection

For detection of coronavirus in an individual, the major technique followed is reverse transcriptase test by Real-Time PCR. As per the protocol, a swab is taken from the nose or the back of the throat and sent to the laboratory. A wide range of specimens (such as swabs, nasal swabs, nasopharynx or trachea extracts, sputum or lung tissue, blood and feces) can be taken [16]. Moving forth the RNA of SARS-CoV-19 is purified and converted into DNA using reverse transcriptase enzyme by following reverse transcription procedure by the addition of desired DNA, nucleotides, primers, DNA building enzyme (DNA polymerases), fluorescent dyes in the small vials. With the help of thermocycler, the PCR duplicates the virus DNA and the dyes bind to the copied virus DNA. After performing a few cycles, a graph can be plotted by the spectrophotometer as fluorescence *versus* number of cycles.

A specialized protocol has been described by Howard Hughes Medical Institute, Cambridge using the CRISPR-based SHERLOCK technique for the detection of COVID-19 using the *cas12* gene [17–19].

Using a simple PCR machine, the scientists of the University of Oxford developed a new detection test. They have tested 16 samples in 90–120 min with 100% accuracy [19].

Pune-based Mylab Discovery Solutions became the foremost Indian firm to receive the approval for the coronavirus diagnosis test kits, called RT-PCR tests (Pathodetect COVID-19) [20].

Abbott Laboratories released molecular point-of-care test to detect novel COVID-19 in as little as 5 min; it contributes to the broad range of diagnostic options needed to combat this infection. Robert B. Ford, President and Chief Operating Officer, Abbott [18–22] stated “With rapid testing on ID NOW, healthcare providers can perform molecular point-of-care testing outside the conventional four walls of a medical facility in outbreak hotspots”.

Home screening test kit which has been approved by the Indian Council of Medical Research (ICMR) and launched by Bione based on IgG and IgM detection tool, takes 5–10 min to obtain the results. The blood samples are collected after pricking the finger of the user using lancet, then the cartridge reads the results from the blood sample [22].

TRANSMISSION BASED ON TEMPERATURE

Scientists from the Massachusetts Institute of Technology (MIT), USA have studied and published a paper on SSRN on 2020 Mar 19, stating that till 21st March, 90% of Coronavirus had transmitted in the regions of temperatures ranging at 3–17°C and absolute humidity ranging at 4–9 g/m³ during the outbreak. However, less than 6% of transmissions took place in countries with average temperatures above 18°C and absolute humidity quite 9 g/m³. Scientists from the University of Maryland's Institute of Virology published a paper on SSRN on 2020 Mar 9, claiming that the Coronavirus particles spread more rapidly between people when the mean temperatures are between 5°C and 11°C and humidity is low [23].

According to the Maryland study, the distribution of significant community outbreaks along restricted latitude, temperature and humidity are according to the behaviour of a seasonal respiratory virus.

Scientists of Spain and Finland published a paper in medRxiv on 2020 March 16, stating that 95% of COVID cases across the planet occurred at temperature ranges of -2°C and 10°C till 10th March 2020.

TREATMENT/CONTROL

As of now none of the antiviral treatments and vaccines proved successful in curing COVID-19. The treatment is dependent on individual symptoms and oxygen therapy is advised as the major treatment intervention in the case of severe infection. Mechanical ventilation is necessary in case of respiratory failure. However, hemodynamic shock support is mandatory for managing septic shock [3].

Intubation and Protective Mechanical Ventilation

Essential precautions are to be taken during intubation by an expert operator who has personal protective equipment (PPE) such as N95 mask or FFP, protective goggles, disposable gown with long sleeve raincoat, disposable double socks and gloves. If required, rapid sequence intubation (RSI) can be performed. Continuous Positive Airway Procedure (CPAP) method should be performed for preoxygenation (100% O₂ for 5 min).

Some More Therapies

Usage of Paracetamol, Azithromycin, Oseltamivir, Lopinavir/Ritonavir [23, 24], Hydrochloroquine, Chloroquine [25–27] and Alpha-interferon are proposed as anti-viral treatments for treating COVID-19, although these are not approved yet. System Corticosteroids for treating viral pneumonia or ARDS are not suggested. Furthermore, unselective or inappropriate antibodies should be avoided.

Preclinical studies suggested that Remdesivir [28] (GS5734)—an inhibitor of RNA polymerase with *in vitro* activity [29] against multiple RNA virus, including Ebola—has shown promising results in a rhesus macaque model of MERS-CoV infection.

In Italy, a study led by the Istituto Nazionale Tumori, focused on the use of tolicizumab. It is a humanized IgG1 monoclonal antibody [30].

Men are More at Risk than Women

In spite of the very fact that males and females are equally infected (51% affected are men), the death rates vary significantly: 2.8% death rate in men and 1.7% death rate in women [31].

This scenario is same among all age groups. From the data of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), both of which were also pathogenic coronaviruses, females tend to have low mortality rates than males. In experiments, mice injected with SARS and MERS revealed that female mice were less vulnerable to infection than male mice. Female

mice became more prone to infection and infection-related mortality by removal of ovaries or blocking estrogen [32, 33]. Protective nature of estrogen in such infections is still being studied by various researchers. Apart from estrogen, the presence of an additional X-chromosome, which carries genes for immunity, plays a major role in the biologic variation between females (who carry XX-chromosomes) and males (who carry one X and one Y chromosome) when it comes to immunologic response to infections.

Vaccine Trials

Moderna, a US firm handling therapeutics, has announced a vaccine with mRNA technology named as mRNA-1273. The vaccine is yet to be approved and is presently undergoing phase 1 trials. Moderna's mRNA technology aims to develop drugs that guide within the body to form proteins to prevent the disease. When the genome sequence of the SARS CoV2 is released Moderna was ready to decode the sequence of a spike protein. They have organised to arrange this sequence in a functional mRNA, that would lead its way to the vaccine [34]. When this vaccine is given to an individual the mRNA reaches the cytoplasm of the cells and with the help of translation would code into spike proteins that are further identified by body cells and would prevent the occurrence of disease.

Entos Pharmaceuticals, a Canadian Biotechnology company, is in the process of developing a DNA vaccine against HCoV [35].

The Serum Institute of India, Pune, India partnered with Codagenix has developed a live attenuated COVID-19 vaccine-viral strain. This viral strain is just like that of the original virus and is capable of producing a potent immune reaction. This research is yet in preclinical phase [36].

In the middle of the coronavirus pandemic painting a daunting picture across the planet, the scientist of University of Hyderabad (UoH) brought a ray hope. A faculty member of the biochemistry department has possibly done a breakthrough for the country and therefore the world by developing a potential vaccine against the deadly coronavirus. Dr. Seema Mishra of UoH has developed a potential vaccine candidate called T cell epitopes against all the Nsps of SARS-CoV-2. These potential vaccine candidates are peptides of coronavirus which will trigger an immune response within the human body to kill those cells harbouring the virus. Dr. Seema has designed these vaccines using the immunoinformatic approach with computational software in such a way that it can be used to vaccinate the whole population.

Experiment Dealing with a Peptide that Could Work as a Potential Drug Blocking COVID-19

A group of pharmacologists from MIT, Massachusetts has formulated a drug candidate that they assume might be a barrier to the ability of coronavirus to invade human cells. The potential analogue could also be a brief fragment of protein or peptide that resembles a protein present on the surface of the human cells.

A post doc in Pentelute's lab said, "Peptides are larger molecules, in order that they can really grip onto the coronavirus and inhibit entry into cells, whereas if you used a little molecule, it's difficult to dam that entire area that the virus is using." Furthermore, "Antibodies even have an outsized area, so those may additionally prove useful. Those just take longer to manufacture and find out."

They have to be altered in order to be effective by staying in the bloodstream for long period. They might be only given intravenously or injected under the skin as they cannot be taken orally.

To develop potential drugs that might block the entry of virus, Genwei Zhang, a researcher in Pentelute's, carried out computational simulations of the docking between the ACE2 receptor and the RBD of the spike protein of coronavirus. These simulations revealed the site where the RBD binds with the ACE2 receptor—where the alpha helix structure of the ACE2 protein is formed.

These simulations give an insight into how atoms and biomolecules interact with one another and the essential part required for such interactions.

Moving forward they have used peptide synthesis technology to rapidly produce 23 amino acid peptide with an equivalent sequence of the ACE2 receptor—alpha helix. In about 37 sec, the linkages between amino acids can be developed by Flow-based Peptide synthesis machine. To obtain a complete peptide molecule that contains 50 amino acids, it takes about 60 min.

A shorter sequence of just 12 amino acids present between the alpha helix, were also synthesized. Both of the peptides were tested by the UV instruments at the MIT Biophysical instrumentation facility that shows the affinity of binding between the two molecules. The shorter peptide displayed minimal binding. In contrast, the longer peptide revealed strong binding to the RBD of spike protein of COVID-19.

In order to test the peptide in human cells and animal model for COVID-19 infection, the original 23 amino acid peptide was sent to a research laboratory at the Icahn School of Medicine, Mount Sinai.

CONCLUSIONS

What We have Observed

A new strain from Coronavirus family emerged into a pandemic during 2019 and 2020. This is because of its new structural morphologies due to mutations as a result of different environmental conditions of different countries, their varied pollution standards and food habits of individuals. Till now more than 30 different strains have been isolated from the beginning of emergence with variations in virulence. Human population became susceptible to the disease due to weakened immunity by age, lifestyle changes and smoking habits. In mild cases, various home remedies can be used to treat the infections. Many countries have failed to control this spread thus leading to recession. Development of vaccines is delayed by lack of sufficient epidemiological studies and resources.

What We Should Acquire

Now we should gain knowledge about how to tackle a pandemic by improvising the scientific research by providing Biological containment facility (BSL-3 followed by BSL-4 laboratories), animal house to maintain animal models for studies before going into human trials. Every state should have required innovative research centre for further studies. The World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) should upgrade the epidemiological studies with latest innovations and technologies such as Bioinformatic studies, Artificial Intelligence, Robotics, and Software Programming. The Ministry of Health and Family Welfare (MoHFW) should directly focus on scientists and researchers rather than permitting a particular research institute with their funding.

How to be Prepared

Medical services have to be extended to every corner of the country followed by increasing the quality of healthcare systems. Industrial food product supply has to be maintained uninterruptedly to prevent food crisis. Slaughtering of animals has to be reduced with increasing *In-Vitro* Meat Production System (IMPS) to control the spread of diseases from animal sources. To maintain the economic stability, we should collaborate scientific theories with software technologies and encourage online medical assistance, drug supplies and diagnostics. To maintain containment facilities, quality testing has to be employed with increasing quarantine centres, a team for maintaining biohazardous samples, large scale production of personal protective equipment, sanitizers, masks and medical provisional.

Declarations

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Conflicts of Interests

Authors don't have any inequality.

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Contributions

All the authors worked on this manuscript by collecting data, plotting graphs and scientific writings, reviewing the format and all other works have been done co-ordinately.

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