

**Exploring *Transmission,*
Pathogenicity related
Mechanisms,
Biomolecular study
&
Worldwide Societal
*Impact of Covid-19.***

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Acknowledgement

I owe a gratitude to the concerned authorities for enabling me to compile this interesting and informative booklet titled- *Exploring Transmission, Pathogenicity related Mechanisms, Biomolecular study and Worldwide Societal Impact of Covid-19.*, for the enthusiastic and the busy Medicos.

An effort is made in this E- BOOKLET to present a brief introduction to emerging and re-emerging pathogens, i.e., coronavirus in humans and animals, its *taxonomic classification, genome organization, its replication, pathogenicity, impact on socioeconomic growth, and drugs* associated with COVID-19.

Although care has been taken while compiling and checking information given in this Booklet to ensure that it is accurate, and none shall be responsible, in any way, liable for contemporaneousness of this information or for any errors, omissions or inaccuracies in this publication.

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Exploring Transmission, Pathogenicity related Mechanisms, Biomolecular study and Worldwide Societal Impact of Covid-19.

1. Introduction.

Coronaviruses are positive-sense RNA viruses with single stranded RNA and non-segmented envelopes.

Recently, genome sequencing confirmed that COVID-19 is similar to SARS-CoV and bat coronavirus, but the major source of this pandemic outbreak, its transmission, and mechanisms related to its pathogenicity to humans are not yet known.

Coronaviruses have been studied for more than 50 years and have infected many species of animals, which include birds and humans, and its first reported strain was isolated from the prototype murine coronavirus strain JHM.

The increasing population, frequent mixing of animals, deforestation, and urbanization have increased the population of other viruses too along with coronavirus.

✚ Coronaviruses belong to the largest group of viruses which are:

- Positive-sense RNA viruses,
 - Have spike-like projections on the surface, and
 - Contain a large unusual genome which has a unique self-replication phenomenon with high rate of mutation and recombination.
- Because of these special characteristics, this virus needs to cross the species barrier and find new hosts to survive and replicate.

✚ In 2005, Susan and Sonia reported an:

- ✓ Avian infectious bronchitis virus (IBV),
- ✓ Bovine coronavirus (BCoV), and
- ✓ Porcine transmissible gastroenteritis virus (TGEV) as the examples of animal viruses which are of great importance in veterinary research methodology.

✚ In 2015, reported severe:

- ✓ Acute respiratory syndrome coronavirus (SARS-CoV),
- ✓ Porcine epidemic diarrhea virus (PEDV), and
- ✓ Middle East respiratory syndrome coronavirus (MERS-CoV) are the best examples of coronaviruses which caused epidemic diseases in animals with huge economic loss.

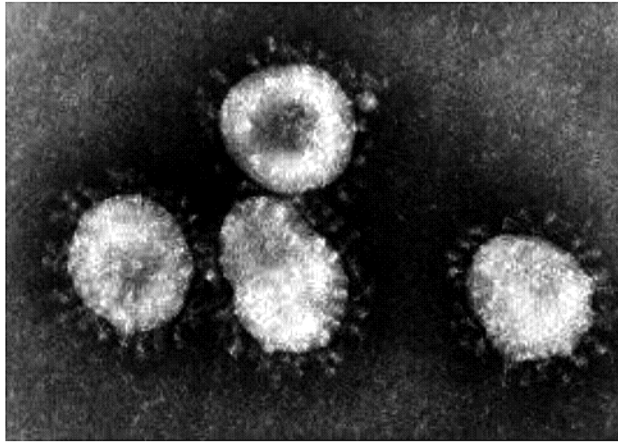
From the last two decades, these viruses caused lethal respiratory infections and serious problems in different classes of mammals and birds which include:

- Humans,
- Dogs,
- Chickens,
- Pigs, and
- Cows.

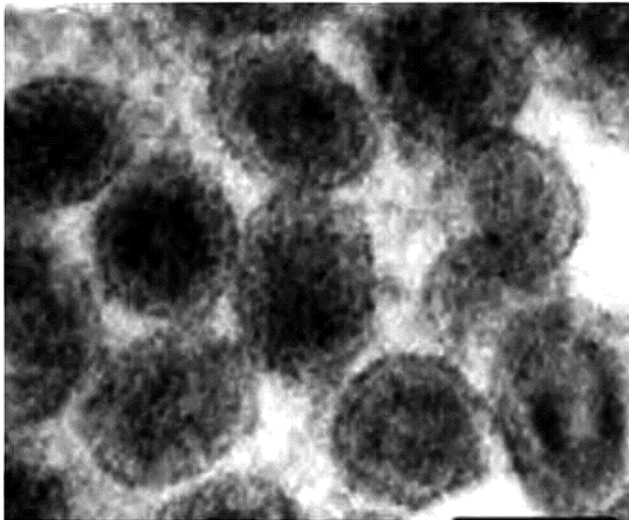
2. Structure & Systematic Classification of Covid-19 virus.

In 1968, Tyrrel et al. coined the name *coronavirus*, which was further derived by cryo-electron tomography microscopy techniques, has a crown-like structure, belongs to the order *Nidovirales* and family *Coronavirinae* which are non-segmented enveloped positive-sense RNA, and contains a large genome of 30 kb in size for RNA viruses.

- The *Nidovirales* order includes families:
 - *Coronaviridae* such as:
 - SARS and
 - PEDV.

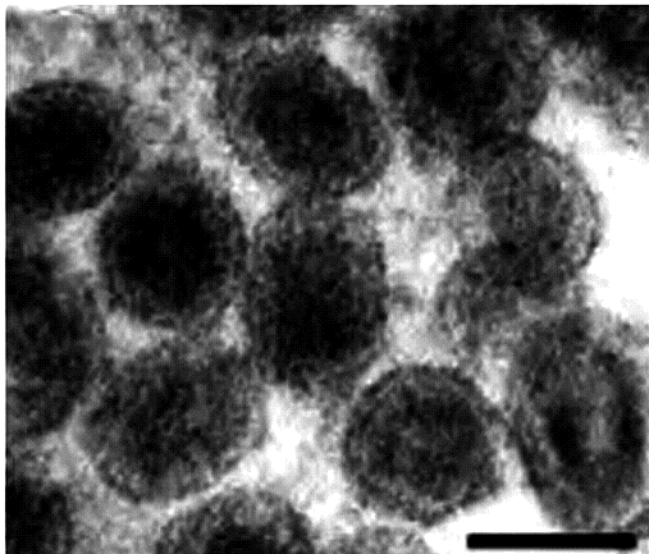


- *Arteriviridae* (swine and equine pathogens),



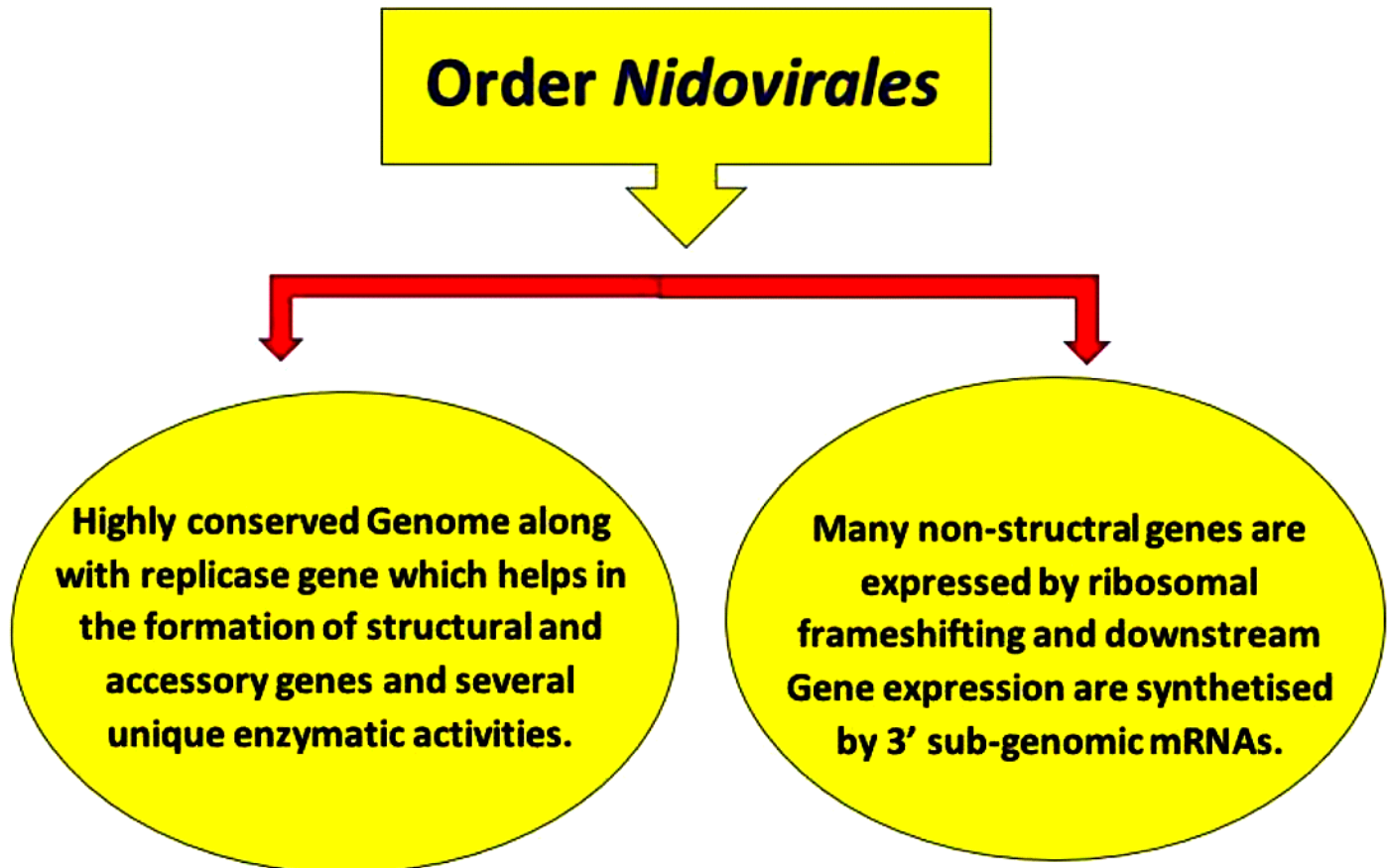
and

- *Roniviridae* (invertebrate viruses).



- The other common characteristics of *Nidoviriales* are shown in Fig. below.

Fig. *Characteristics of Nidoviriales family of coronavirus.*



The major differences in the family of *Nidovirus* are in its **number, sizes, and type of structural proteins** which leads to **morphological and structural changes of the virus structure.**

Coronavirus has always been in controversy as it belongs to **SARS-CoV.**

✚ However, in 2004, Goebel et al. and Gorbalenya et al. listed it in *Group II* which is tabulated in Table below.

Group	Host	Virus	Diseases	Cellular responses
I (Animal Pathogens)	Human	229E and NL-63	Respiratory infections	Human APN and ACE2
	Pig	TGEV, PRCoV	Respiratory and enteric infection	Porcine APN
	Cat	Canine coronavirus, FeCoV, FIPV	Respiratory, enteric, and neurologic infection, and hepatitis	Canine and feline APN
II (Veterinary Pathogens)	Human	OC43, HKU1, and SARS-CoV	Respiratory infection, possibly enteric infection	Neu5,9Ac2-containing moiety
	Mouse	MHV	Enteric and neurologic infection and hepatitis	Murine CEACAM1
	Rat	Sialodacryoadenitis coronavirus	Neurologic infection	Not determined
	Pig	Hemagglutinating encephalomyocarditis	Respiratory, enteric, and neurologic infection, and hepatitis	Neu5,9Ac2-containing moiety
	Cow	BCoV	Enteric infection	Neu5,9Ac2-containing moiety
III (Avian Pathogens)	Turkey	Turkey coronavirus	Respiratory and enteric infection	Not determined
	Chicken	IBV	Respiratory infection, hepatitis	Not determined

✚ In :

Feral pigeon,



- *Graylag goose*, and



- *Mallard*,



coronavirus sequences had been detected using reverse transcription and phylogenetic analysis of replicase enzyme and nucleocapsid sequences whose cellular receptors are not determined yet.

- ✚ *Coronavirus* is rounded, enveloped, and non-segmented with approximately 80 to 125 nm in size.

- It consists of *positive-sense RNA* of genome size of ~ 30 kb and has *four structural proteins* which are encoded within the *3' end of the viral genome*.

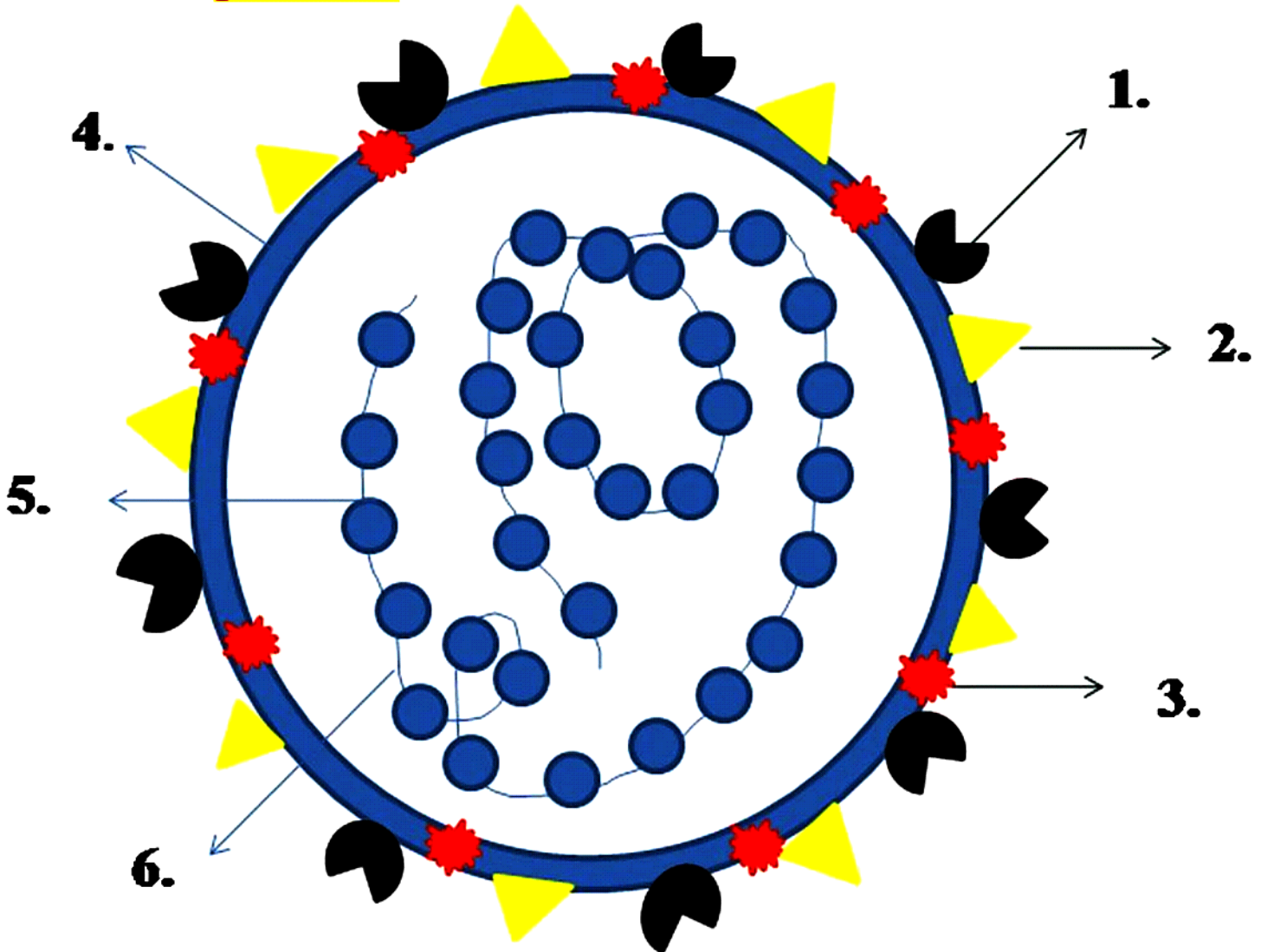


Fig. *Depicts the structure of respiratory syndrome causing human coronavirus.*

(1) Spike (S), (2) Membrane protein (M), (3) Envelope protein (E), (4) Lipid bilayer, (5) Nucleocapsid (N), (6) RNA

- The *nucleocapsid protein (N)* is *helically symmetrical* which forms *a helical capsid* inside

the *viral membrane* and contains three viral proteins.

- There is *club shape-like spike* (S) projections of ~ 150 kDa type I glycoproteins, forming *peplomers* from the surface of *virion*, which gave them crown-like structure which is depicted by electron microscopy.
- The virus also contains *membrane* (M) proteins which are extended three times to the outer surface, a *small membrane protein* (E), and *short N-terminal ectodomain* along with *cytoplasmic tail* and a *highly hydrophobic protein*.

The detailed classification of coronavirus group with its *host, viruses, diseases, and cellular responses* of CoV is given in **Table above** and the **detailed view of structural genes of coronavirus is summarized** in **Table below** on **page no.15**.

3. Organization of Genome & Life Cycle.

The **spike protein in coronavirus** plays an important role in the entry of virus for its attachment with its receptor and also determines the tissue tropism of the virus.

- This entry is **not dependent on pH and its cell-to-cell spread**, so it is believed that **it occurs directly through the plasma membrane** although some viruses may utilize endosomal route **but it is not through endosomal route for coronaviruses.**

✚ In 1995, **Holmes and Compton** identified *carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM 1)* as **first CoV receptor binding domain at the N-terminal** which was utilized by *murine coronavirus (MHV)* whereas **SARS-CoV** has receptors at the *C-terminal of S1 fusion protein*.

- As the virus enters into the cell, the 5' end of the RNA genome which contains the open reading frames *1a and 1b (ORF 1a and 1b)* is translated into poly protein 1a (pp 1a) (frameshift mechanism which occurs at a very high speed) and *pp1ab ORF 1a* codes for one to two *papain-like proteases* and *picoronavirus* (group of **related RNA viruses** which infect vertebrates including mammals and birds) which.

- ADP-ribose 1-phosphatase further helps in the formation of mature replicase proteins through *pp1a* and *pp1ab* activity is also encoded in the *X domain of ORF1* and a *RNA-dependent RNA polymerase (RdRp)* and a *helicase* are encoded in the X domain of 3' to 5' exonuclease *ORF 1a*.
- Also, *cyclic phosphodiesterase* putative enzymatic is encoded downstream in *ORF 2a*.
- Along with this, multiple other enzymes like *poly (U)-specific endoribonuclease (XendoU)* and (putative) *S-adenosylmethionine-dependent ribose 2_-O-methyltransferase* play an important role in metabolism of coronavirus *RNA* and with the host cell process.
- The replication of genome leads to the full-length negative-strand *RNA* synthesis (present in low concentration) which serves as template (*mRNA 75–78 nt*) for transcription along with leader and lagging strand at 5' and 3' ends of *mRNA*.
- The synthesis of positive and negative strands which involves a unique discontinuous transcription mechanism is still not completely understood.
- The *replicase enzyme* is translated from the 5'-end of the genomic *RNA*, and *ORFs* are mediated by an internal ribosomal entry site.

- The *endoplasmic reticulum* forms a compartment with *M* and *E* proteins of Golgi bodies which are near the *intracellular membrane*, and is an *actual site of budding*.
- During assembly, after budding process the intracellular and plasma membrane having spike protein interacts with transmembrane of *M* protein and *N* protein which forms helical structures with genomic RNA.
- The *nucleocapsid* interacts with *M* protein and budding into vesicles takes place from where the virus is transported to cell surface, and it leaves the cell at this stage.

Table. Detailed view of structural genes of coronavirus.

<i>Structural genes</i>	<i>Composition</i>	<i>Functions</i>
Nucleocapsid (N)	<ul style="list-style-type: none"> • Two separate domains, i.e., N-terminal and C-terminal. • Highly phosphorylated, TRSs and genomic packaging signals are two specific RNA substrates, consists of nsp3 (component of M protein and replicase complex) 	<ul style="list-style-type: none"> • Domains required to bind RNA, phosphorylation leads to a structural change which increases the affinity of viral RNA versus non-viral RNA and this viral genome binds with N protein forming beads like conformation. • Genomic packaging signal bind specifically to the second or C-terminal RNA binding domain. • Protein interaction helps in the formation of replicase-transcriptase complex (RTC) and packaging of encapsulated genome into the viral particles
Membrane (M)	<p>Most abundant, small in size (~ 25–30 kDa), 3 transmembrane domain structural protein, contains small N- and large C-terminal glycosylated ectodomain which ranges from 6 to 8 nm inside the virus</p>	<ul style="list-style-type: none"> • Helps to give shape to virion and exists in dimer from different conformations, so that membrane curvatures and nucleocapsid can bind very well. • Most of the M protein does not contain signal sequences although they are translationally inserted in the endoplasmic reticulum membrane.
Envelope (E)	<ul style="list-style-type: none"> • Present in small amount (~ 8–12 kDa), transmembrane protein in the virion. • Highly divergent but consists of a 	<ul style="list-style-type: none"> • Membrane topology of E protein is not completely resolved. • Helps in assembly and release of the virus and ion channel in SARS-CoV; this protein is required for pathogenesis but not for viral replication

Contd.

	<p>common architect.</p> <ul style="list-style-type: none"> Also consists of a <i>N-ectodomain</i> and <i>C-endodomain</i> terminal with ion channel activity 	
Spike (S)	<p>Heavily N-linked glycosylated protein of ~ 150 kDa which uses N-terminal sequence for the functioning to the ER, consists of S glyco-trimeric class I fusion protein in which S1 helps in the formation of the large receptor-binding domain and S2 in stalk of the spike molecule</p>	<ul style="list-style-type: none"> Helps in the formation of homotrimers encoded by S protein spike like structure on the outer surface of the virion, helps in attachment to the host receptor.
Hemagglutinin-esterase (HE)	<p>Subset of β-coronaviruses, acts as a hemagglutinin which binds sialic acids on the surface of glycoproteins and also contains acetyl-esterase activity</p>	<ul style="list-style-type: none"> Enhances murine hepatitis virus (MHV) neurovirulence and the S protein-mediated cell entry through which virus spread through mucosa. It is also used against tissue culture whose function is still unknown.

4. Pathogenicity.

It is well known that *SARS-CoV-2* induces clinical spectrum from asymptomatic forms to severe respiratory failures requiring mechanical ventilation and treatment in

intensive care unit to fatal cases of sepsis and multi-organ dysfunction syndromes.

The pathogenic mechanisms underlying the most common serious manifestation, i.e., virus-produced pneumonia characterized mainly by:

- Fever,
- Cough,
- Sore throat,
- Fatigue,
- Headache, and
- Shortness of breath, are very complex.



Infection with SARS-CoV-2 can induce an extensive immune response in the host organism leading in some cases to massive tissue damage.

- One of the most important players in this reaction is *interleukin-6 (IL-6)*, as this cytokine initiates a *series of inflammatory events*.
- Besides this, elevated levels of other inflammatory cytokines including:
 - Interleukin-2,
 - Interleukin-7,
 - Interleukin-10,
 - (IL-2, IL-7, IL-10), and
 - Tumor necrosis factor- α (TNF- α) have also been reported in the laboratory analyses of

patient's plasma being related to disease severity.

- *Viral pneumonia* appears typically bilaterally, involving mostly the lower lobes, and is more severe in elderly patients older than 70 years of age and those suffering from various comorbidities.

However, most children and younger adults with *SARS-CoV-2* present mild to moderate flu-like symptoms, having a good prognosis.

In addition to the aforementioned clinical manifestations, some patients have complained also about gastrointestinal problems, such as vomiting and diarrhea.

The illustrations of reservoirs and transmission CoV strain are shown in Fig. below.

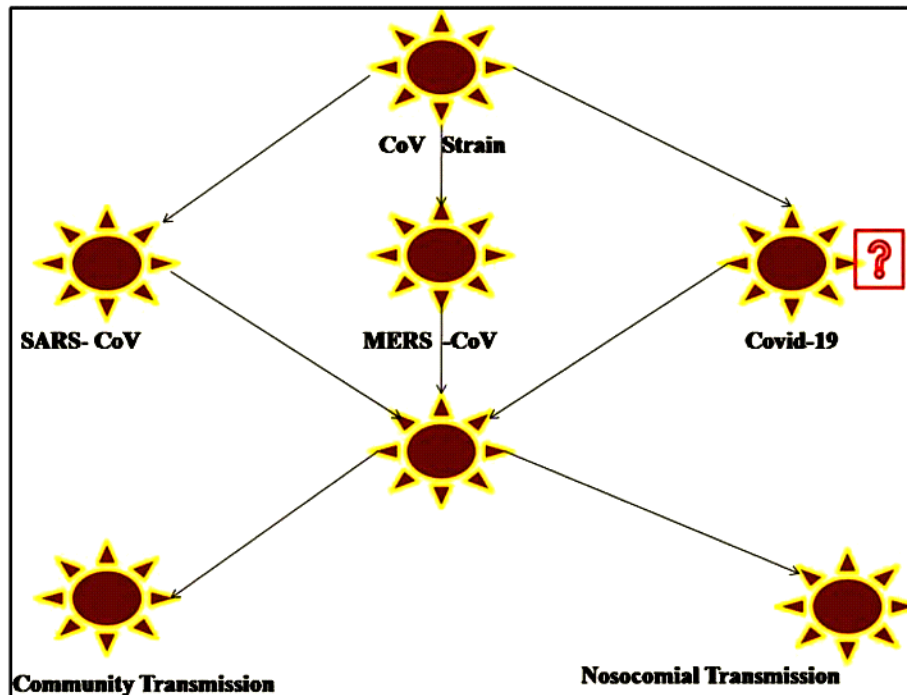


Fig. Illustrations of Reservoirs and Transmission CoV Strain.

5. Transmission.

The virus can enter the body through the mucous membranes, particularly nasal and larynx mucosa, passes the respiratory tract, reaches to the lungs, and replicates rapidly.

- ✚ Although there are several possible transmission ways, respiratory droplets spread by coughing or sneezing is the principal route for virus distribution, whereas it can occur also by means of asymptomatic persons.
 - Getting the infection usually necessitates a direct close contact (within 2 m) with a virus-positive person for a prolonged period of time.
 - In addition, it is possible that *SARS-CoV-2* can spread also via fecal–oral transmission, as the virus has been detected in the stool and urine of patients.
 - Incubation period for COVID-19 has been reported by WHO to be between 2 and 10 days.
 - After entering the body, the virus can potentially attack the target tissues expressing angiotensin-converting enzyme 2 (ACE2), including the:
 - Lungs,
 - Heart,
 - Kidneys, and

- Gastrointestinal tract.
- Despite the first recovery, the virus typically induces a second attack, associated with the aggravation of patient's condition about 7 to 14 days after onset.
- The median time from the onset of disease to the most serious clinical outcome, death, has been demonstrated to be 14 days.

6. Diagnostic Techniques

The symptomatic presentation of COVID-19 patients is non-specific and does not warrant precise diagnosis of patients.

- This is mainly attributed to the clinical symptoms which may be a manifestation of respiratory infections.
- This is supported by findings from the study which mentioned that 89% of patients presented with fever later when hospitalized in comparison with 44% of patients who presented with fever upon entering hospital.
- In view of the *limitations of symptomatic diagnosis*, *CT scans and nucleic acid testing* are currently

being used widely for COVID-19 screening and diagnosis.

- The strength of molecular techniques for precise diagnosis is attributed to their capability of identifying target specific pathogens.

6.1. CT Scan

In view of short supply of COVID-19 detection kits and false-negative rate of RT-PCR, CT scans are also temporarily being used for COVID-19 clinical diagnosis.

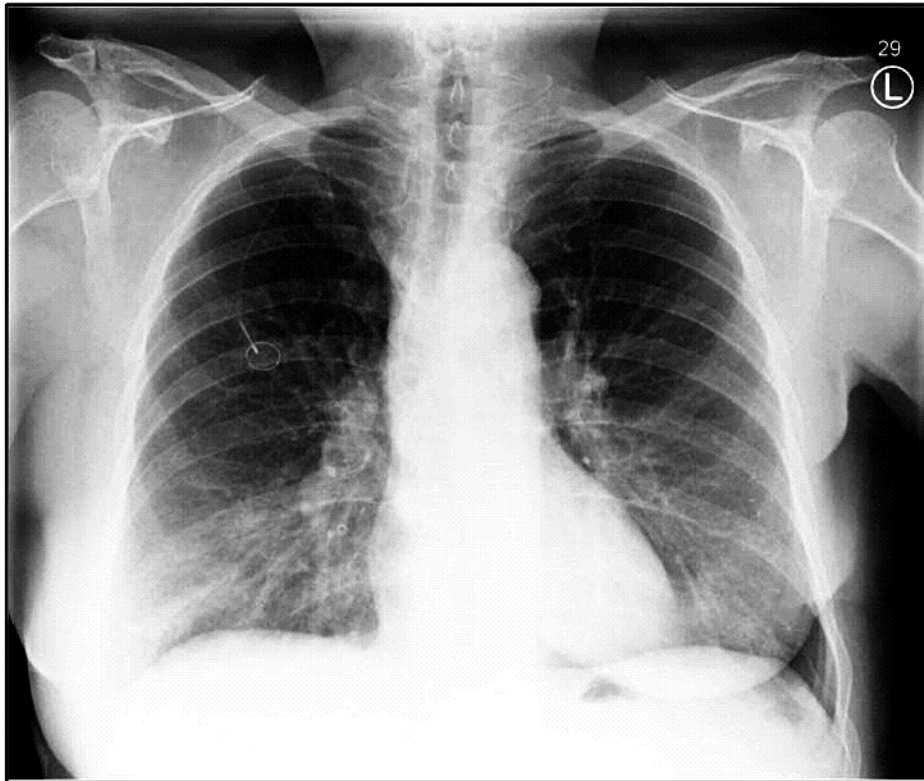
The non-invasive chest CT scans are cross-sectional images captured based on measurement of *X-rays* at different angles across the patient's chest and analyzed by radiologists for abnormal presentation.

Imaging studies using CT scans in COVID-19 patients presented with diverse features in scans which mainly varied depending on the time of onset of symptoms and stage of infection.

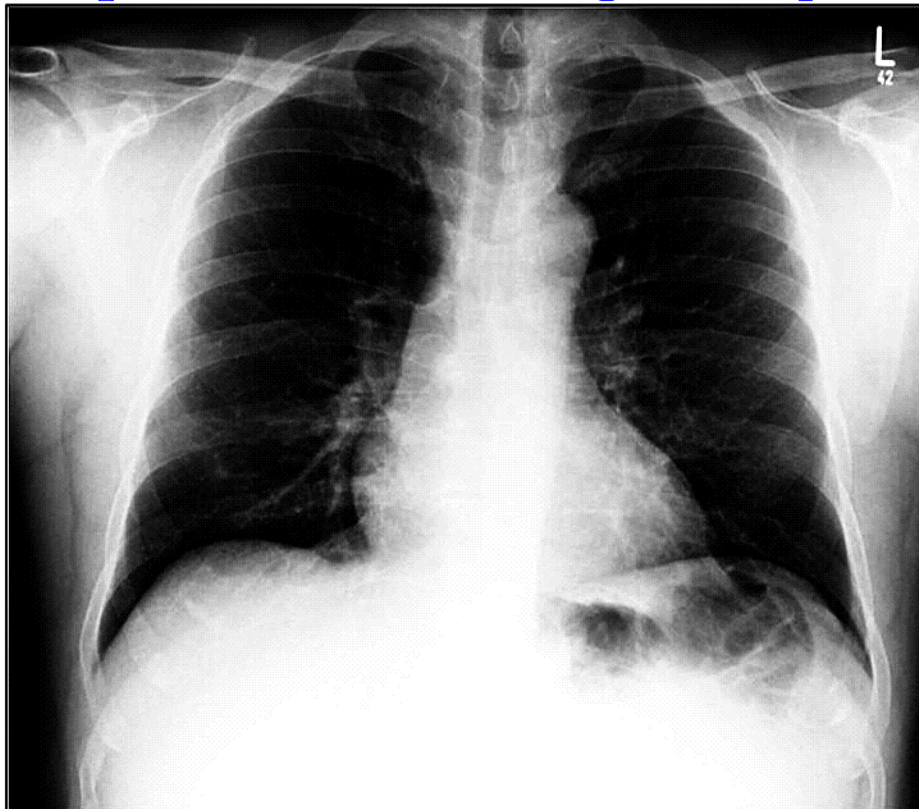
It has been found that patients presenting with early stage of COVID-19 were diagnosed with normal findings in CT scan in 56% of the COVID-19 patients and had lung involvement after 10 days of infection or onset of symptoms.

- The most commonly observed hallmark of COVID-19 manifestation included:

○ Consolidation of lungs and



○ Peripheral and bilateral ground-glass opacity.



It was reported that the **ground-glass opacity** was **more evident 0–4 days after onset of symptoms**.

As the infection progressed, **it led to irregular paved stone pattern followed by lung consolidation** (solid or fluid in compressible lung tissue).

Interestingly, *CT scans* have also been the method of choice in view of false-negative rate of RT-PCR and 86–98% sensitivity.

A major limitation of using CT scans extensively for COVID-19 diagnosis is **its low specificity which overlaps with viral presentations like pneumonia.**

6.2. Nucleic Acid Test (RT-PCR)

The primary method for diagnosis of COVID-19 is *nucleic acid* testing technique which is based on *RT-PCR*.

- **In this method, according to laboratory testing for COVID-19, the suspected human samples are taken from:**
 - ***Upper respiratory tract* such as:**
 - **Nasopharyngeal swab,**
 - **Nasal aspirate, or**
 - **Paryngeal swab or the**
 - ***Lower respiratory tract* such as:**
 - **Sputum,**

- Tracheal aspirate for *RNA* extraction followed by reverse transcription and *cDNA amplification* of a specific region.
- The primers for *RT-PCR* are designed against the conserved sequence of *SARS-CoV-2 viral genome with RdRP in the ORF1ab*, **envelop protein gene (E)** with high analytical sensitivity with a detection limit of as low as 3.6 and 3.9 copies/reaction, respectively, in both primers and **nucleocapsid protein gene (N)** with detection limit as 8.3 copies/reaction with poor analytical sensitivity.
- The *RT-PCR* method is a two-step method in which the **single-step RT-PCR is quick**, currently being used by the **USA** for screening **COVID-19** patients with cycling conditions and recommended by **CDC, Atlanta, GA, 2020**, and also provides the positive control *nCoVPC sequence* for reference and adequate to address the increased need for **quick and timely COVID-19 detection**.

On the other hand, the **two-step assay is more sensitive than one-step assay**; however, its main limitation is the requirement of standardization of **additional experimental parameters** and also it is more time consuming.

A number of different SARS-CoV-2 RT-PCR detection kits have been marketed from different

companies and research groups and are summarized in Table below.

Detection platform	Sample type	Number of samples	Technology	Detection technology
Nucleic acid testing				
RT-PCR	Throat swabs	1014	RT-PCR	Reverse-transcription amplification and fluorescent signal detection
RT-PCR	Oropharyngeal/nasopharyngeal swabs	176	RT-PCR	Reverse-transcription amplification and fluorescent signal detection
RT-PCR	Oro-nasopharyngeal swabs or endotracheal aspirate	32	RT-PCR	Reverse-transcription amplification and fluorescent signal detection
RT-PCR	Placental and fetal membrane samples	11	RT-PCR	Reverse-transcription amplification and fluorescent signal detection
RT-PCR	Nasopharyngeal, throat swab, sputum, saliva	59	RT-PCR	Reverse-transcription amplification and fluorescent signal detection
RCA	Serum	7	Rolling circle amplification	Circular primer repeated amplification
RPA	Fecal and nasal swabs	30	RPA	DNA blinded with forward and reverse primers and amplified
NASBA	Nasal swabs	138	REAL TIME-NASBA	RNA target—transcription amplification
RT-LAMP	Nasopharyngeal aspirates	59	LAMP	Reverse transcriptase isothermal cDNA amplification
RT-LAMP	Throat swabs	16	LAMP	Reverse transcriptase isothermal cDNA amplification
RT-LAMP	Throat swabs	56	LAMP	Reverse transcriptase isothermal cDNA amplification
LAMP	Throat swabs	53	LAMP	Isothermal DNA amplification
ILACO	Not specified	248	LAMP	Isothermal LAMP
CRISPR	Nasopharyngeal swabs	384	RT-RPA	SHERLOCK fluorescence multiplexed signal detection
CRISPR	Serum	110	RPA	CRISPR/Cas9-mediated lateral flow nucleic assay (CASLFA)-PCR
Magnetic bead	Stool	17	Magnetic	Magnetic bead isolation for PCR detection
Quantum dot barcode	Serum	72	Barcode	RPA detection of viral DNA captured using multiplexed quantum beads
Paramagnetic bead	Serum	12	Magnetic biosensor	Protein targets—magnetic separation
Smartphone dongle	Blood	96	ELISA	ELISA operated through microfluidic-based cassette
Protein testing				
Rapid antigen test	Serum	117	Lateral flow	Colorimetric signal produced by gold-coated particles if SARS-CoV-2 positive on paper
ELISA	Serum	30	ELISA	Colored product from enzymatic reaction
Biobarcode assay	Serum	18	DNA-assisted immunoassay	Gold nanoparticle conjugated DNA is amplified followed by signal detection
SIMOA	Serum	30	Digital ELISA	Digital readout of colored product from enzymatic reaction

✚ The other method of nucleic acid testing is *isothermal amplification test* because of **its high specificity** and is conducted at **a single temperature**, i.e., *reverse transcription-loop-mediated isothermal amplification (RT-LAMP)*.

- The major limitation of *RT-LAMP* is optimization of specific reaction condition and primer combination to be used in view of which other isothermal techniques for amplification are being looked into.

✚ In addition, *SHERLOCK*, a *Cas13a* ribonuclease based *RNA sensing detection strategy*, is also being used with SARS-CoV-2 detection protocol.

- This is further being explored for other *Cas13a*-based detection tests for SARS-CoV-2 detection.

6.3. Serological testing based on Protein Quantification.

According to WHO (2020), the primary priority is to improve patient screening with integration of nucleic acid testing and serological testing based on protein quantification.

- The main advantage of protein testing is time-point-based screening from diagnosis to recovery which is **not possible with nucleic acid testing**; it is

cost-effective and can be implemented in rural areas without instrumental infrastructure facilities.

- For protein testing, the levels of viral protein antibodies are used for detection which provides a larger window for detection in comparison with viral load with fluctuates from initial weeks to later.

However, a major challenge with development of serological tests was to address the issue of SARS-CoV-2 antibody cross-reactivity against other known strains of coronavirus.

- High cross-reactivity frequency was observed when 15 COVID-19 plasma samples were tested against *S protein of SARS-CoV and SARS-CoV-2*.

Different serological tests are being developed for viral specific testing.

✚ Zhang et al. used the *nucleocapsid protein SARS-CoV-2 Rp3* and used *ELISA* for detection of *immunoglobulin M (IgM) and immunoglobulin G (IgG)* in serum of COVID-19 patients.

✚ Xian et al. also detected *SARS-CoV-2 IgM* and *IgG antibody* levels.

✚ In an interesting study, *COVID-19-infected* patients were reported to have high *D-dimer and C-reactive protein (CRP)* levels and low levels of:

- Blood platelets,

- Leukocytes, and
- Lymphocytes.

7. Major Challenges with Nucleic Acid Testing and CT Scan

COVID-19 is presently being screened using CT scans and diagnosed with RT-PCR worldwide. However, both techniques have shortfalls.

A major limitation of CT scan is the requirement of technical expertise to perform and analyze scans; it is expensive and cannot precisely diagnose COVID-19.

- With *RT-PCR*, the major challenge at this time is the development and availability of *COVID-19 detection kits* which is falling short in view of the exponential increase in patient infection rate.
- Second, lack of appropriate infrastructure and *RT-PCR instruments* in medical hospitals in sub-urban and rural areas are to comprehend high sample throughput.
- Next, as *RT-PCR* is based on detection of *SARS-CoV-2 RNA*, there have been cases reported where an asymptomatic patient recovered from *SARS-CoV-2 infections* and hence *RT-PCR* was not able

to detect previous infection or cases where patients were in incubation state when samples were taken for screening and developed symptoms later on.

Hence, using these **two techniques simultaneously** may help to achieve a more accurate diagnosis of *COVID-19 patients*.

- Besides these techniques, *other rapid detection technologies* are also being investigated **to address these limitations of SARS-CoV-2 detection.**

8. Search for viable Therapeutics for COVID-19.

As COVID-19 pandemic has entered a dangerous new phase and wreaking havoc, the world is trying to discover approaches to slow the spread of the novel coronavirus and to discover viable medications.

It will prompt the decrease of burden on the healthcare system of the nation by restricting the number of individuals who are seriously sick by *COVID-19* and will diminish the span of infection carriage so as to confine the transmission in the network.

So, there is an **earnest requirement for therapeutics focusing on SARS-CoV-2.**

Shockingly, there are no FDA-approved drugs for COVID-19 yet; however, they have made a unique crisis program for potential treatments, the *coronavirus treatment acceleration program (CTAP)*.

It utilizes each accessible strategy to move new medications to patients as fast as could be expected under the circumstances while simultaneously seeing if they are useful or harmful (*FDA 2020*).

At present, treatment provided to the affected people is mostly symptomatic and the critically ill individuals are provided with organ support.

Utilization of old antiviral medications will be an intriguing technique on account of *information on security profile, reactions, and phonology, and medication communications* are notable.

Hence, a portion of the significant medications that may help in the fight against COVID-19 is being investigated.

(i) Chloroquine/Hydroxychloroquine

✚ A recent paper revealed an inhibitory impact of *remdesivir* (a new antiviral medication) and *chloroquine* (an old antimalarial medication) on the development of SARS-CoV-2 in vitro.

- Thus, following the **in vitro outcomes**, 20 clinical examinations were propelled in a few *Chinese emergency clinics*.
- Results demonstrated the predominance of *chloroquine* (500 mg chloroquine two times per day for 10 days) contrasted with treatment of the control group as far as **decrease of pneumonia, length of indications, and deferral of viral freedom**, all without extreme reactions.
- Similarly, *hydroxychloroquine* (an analogue of chloroquine) has been **shown to have an inhibitory effect on SARS-CoV activity in vitro**.
- A few other pre-clinical in vitro examinations propose that **both chloroquine and hydroxychloroquine have activity against SARSCoV-2, despite the fact** that one in vitro investigation proposes that *hydroxychloroquine might be stronger* than *chloroquine* and **displayed a higher in vitro antiviral impact as compared with chloroquine**.
- Further, *hydroxychloroquine* **clinical welfare profile** is better than that of *chloroquine* (during long haul use) and **permits higher daily dose** and has fewer apprehensions about drug–drug interactions.

- Both medications are accounted for to hinder significant viral replicating enzymes like *viral DNA and RNA polymerase* and processes, such as:
 - Viral protein glycosylation,
 - Virus assembly,
 - New infection molecule transport, and
 - Infection discharge.
- A few reports proposed that these medications may lead to:
 - Inhibition of *angiotensin-converting enzyme 2 (ACE2)* cell receptor,
 - Acidification at the *surface of the cell membrane* impeding fusion of the virus, and
 - Immunomodulation of *cytokine release*.

(ii) Remdesivir

A nucleoside (adenosine) analogue remdesivir is a broad-spectrum antiviral agent.

- It was produced by *Gilead Sciences* in 2017 as a treatment for *Ebola infection*.
- In vitro studies demonstrated that *remdesivir* can repress coronaviruses, for example:
 - SARS-CoV and
 - MERS-CoV replication.

- Information propose *remdesivir* represses movement of:
 - SARS-CoV,
 - MERS-CoV, and
 - Bat CoV strains that can replicate in human epithelial cells and acts as an intermediate channel by means of *human CoV receptors*.
- *Remdesivir* has indicated prophylactic and remedial adequacy against 2002 SARS-CoV in a mouse model.
- It had been recommended that *remdesivir* may be a possibility for the treatment of patients with COVID-19.
- In pre-clinical trials, *remdesivir* has demonstrated noteworthy activity against coronavirus and a high genetic barrier to resistance.
- In vitro studies have also shown that *remdesivir* exerts intense antiviral action against a clinical isolate of *SARS-CoV-2*, given the broad-spectrum anti-COV action of *remdesivir* that were shown in pre-clinical investigations.
- In a case report, *remdesivir* treatment was begun intravenously on day 7 of a patient with COVID-19.

- It was observed that 68% of patients demonstrated clinical improvement when treated with *remdesivir*.
- *Remdesivir* acts as an inhibitor of RNA-dependent RNA polymerases.
- It is reported to compete with *adenosine triphosphate* for incorporation into nascent viral RNA chains.
- When fused into the viral RNA at position i , it ends RNA amalgamation at position $i + 3$.
- Since *RDV-TP* does not cause quick chain end (i.e., three extra nucleotides are joined after *RDV-TP*), the drug appears to evade proof-reading by viral exoribonuclease (a catalyst thought to extract nucleotide simple inhibitors).

(iii) HIV Protease Inhibitor medicines

A randomized, controlled, open-label trial on hospitalized patients with affirmed SARS-CoV-2 disease was directed to check the adequacy of two HIV Protease Inhibitor medicines, i.e., *lopinavir and ritonavir*, toward *SARS-CoV-2* infection.

- Based on prior in vitro and animal model examinations, both these medications have

indicated action against coronaviruses (*SARS-CoV* and *MERS-CoV*).

- Clinical improvement was seen in patients treated with *lopinavir* and *ritonavir*; however, no distinction was noted in the duration of viral shedding after treatment.
 - Both these medications are reported to bind to M^{pro} , a key enzyme for coronavirus replication and help in suppression of coronavirus action.

(iv) Favipiravir

Another broad-range antiviral medicine, favipiravir, with known *in vitro* action against RNA viruses is clinically under scrutiny for treatment against SARS-CoV-2 disease (*Peking University 2020*).

- Favipiravir is a RNA-dependent RNA polymerase inhibitor that represses viral RNA synthesis.

(v) Azithromycin

In a clinical trial, azithromycin was also used in combination with *hydroxychloroquine* to prevent bacterial contamination in patients suffering from COVID-19.

- Initial results show the potential advantage of azithromycin as an adjunct therapy.

- **Previously, *azithromycin* has also been utilized as an adjunct therapy in patients with MERS-CoV in combination with antiviral treatment.**
- **It may stop bacterial infection; furthermore, *macrolides* have *immunomodulatory properties* to be used as adjunct therapy.**
 - ***Macrolides* have demonstrated *immunomodulatory properties* in pneumonic inflammatory disorders, which may down control provocative reactions and lessen the over-the-top cytokine production related with respiratory viral contaminations.**
- ***Azithromycin* may help in lessening *chemotaxis* of *neutrophils (PMNs)* to the lungs by hindering *cytokines (i.e., IL-8)*.**

(vi) Teicoplanin

Another *glycopeptide* antibiotic, *teicoplanin*, a routinely utilized anti-microbial to treat bacterial contamination, was seen as dynamic in vitro against SARS-CoV and has joined the rundown of particles that could be utilized as restorative agent against ***COVID-19***.

- **This antibiotic, as of now utilized in the treatment of *Gram-positive bacterial disease*, particularly**

in *Staphylococcal* infections, has just demonstrated adequacy against different infections, for example:

- Ebola,
- Flu virus,
- Flavivirus,
- Hepatitis C virus,
- HIV virus, and on
- Coronavirus (MERS-CoV and SARS-CoV).

(vii) Inflammatory cytokines

Patients with COVID-19 have demonstrated expanded plasma convergences of *inflammatory cytokines*, for example:

- TNF- α and
- IL-2, 7, and 10, particularly in ICU patients, which suggested that a *cytokine storm* happened.

(viii) Tocilizumab

In light of these discoveries, an *interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody* named *tocilizumab* may prove to be successful for *COVID-19*.

- In this way, patients analyzed as critical COVID-19 were given *tocilizumab* treatment.

- Patients received standard treatment as per treatment protocol for COVID-19 in combination with *tocilizumab*.
 - The results with *tocilizumab* treatment were promising.
 - The temperature of the considerable number of patients came back to normal rapidly.
 - The respiratory capacity and every other manifestation improved amazingly.
 - Among these 21 patients, 20 patients have been recouped and released within 14 days post-*tocilizumab* treatment.
 - *Tocilizumab* hinders *IL-6*-interceded motioning by competitively binding to both solvent and film bound *IL-6 receptors* (*sIL-6R* and *mIL-6R*).

(ix) Sarilumab and Siltuximab.

Another interleukin-6 (IL-6) receptor-inhibiting monoclonal antibodies, namely, *Sarilumab* and *Siltuximab*, are recommended for *COVID-19*, as it has been accounted for to help in charge of *cytokine discharge disorder* which is a segment of extreme cases in *COVID-19* patients.

- An investigation of 21 patients with COVID-19 prompted pneumonia/ARDS was being examined who received treatment with *siltuximab*.

(x) *Baricitinib*

Recombinant human interleukin-1 (IL-1) receptor antagonist *anakinra* and januskinase (JAK) inhibitor *baricitinib* answered to work in cytokine discharge condition are being assessed for its adequacy against COVID-19 (Swedish Orphan Biovitrum 2020).

- *Anakinra* also acts to the local interleukin-1 receptor adversary (*IL-1Ra*) by seriously hindering the authoritative *IL-1*, explicitly *IL-1alpha* and *IL-1beta*, to the interleukin-1 sort 1 receptor (*IL-1R1*).
- *IL-1* is a genius incendiary cytokine that intervenes different fiery and immunological reactions, including actuation of *IL-6* (Swedish Orphan Biovitrum 2018), while *Janus kinases* are intracellular chemicals that transmit signals emerging from cytokine or development factor receptor communications on the cellular membrane to impact cell procedures of invulnerable cell capacity and hematopoiesis (Olumiant 2019).

(xi) Leronlimab

Another *monoclonal antibody*, namely, *leronlimab*, answered to improve insusceptible reaction while relieving *cytokine storm* is additionally assessed for potential treatment of COVID-19.

(xii) Convalescent plasma

- *COVID-19* convalescent plasma is not expected for prevention of the disease.
- Clinical patients are treated with plasma gathered from people who have recuperated from COVID-19 that may contain antibodies to SARS-CoV-2 for clinical preliminaries (FDA 2020).
- Rousing outcomes were achieved in patients who were administered convalescent plasma.
- After *plasma imbuement*, body temperature normalized inside 3 days in four of five patients.
- *Sequential organ failure assessment score* diminished and PAO_2/FIO_2 increased inside 12 days.

The job of healthful enhancements for the treatment or prevention of COVID-19 is obscure.

A few enhancements are under scrutiny in combination with other treatment modalities (e.g., zinc,

nutrient C, nutrient D) for both treatment and prophylaxis (**Progena Biome 2020**).

As there is no approved drug for COVID-19 disease and it will require some investment for potential immunization improvement, along these lines, **it is the ideal opportunity for all the residents to hold hands together to battle against coronavirus by rehearsing self-cleanliness and social distancing.**

9. Impact of Temperature and Humidity on Coronavirus.

COVID-19, caused by SARS-CoV-2, subsequently spreads to many other regions in the world through global travel.

Because of geographical proximity and significant travel connections, epidemiological modeling of the epicenter predicted that regions in:

- Europe,
- America, and
- Southeast Asia would follow *Wuhan and China* in the epidemic.

Temperature and Humidity are known factors in *SARS-CoV, MERS-CoV, and influenza* survival, new outbreaks, and the increase in the risk of infection.

Besides potentially prolonging half-life and viability of the virus, other potential mechanisms associated with *cold temperature* and *low humidity* include:

- Stabilization of the droplet and
- Enhanced propagation in nasal mucosa, as has been demonstrated with other respiratory viruses.

⊕ Although most studies have focused on *relative humidity* that can be affected by *temperature*, few focused on specific humidity to assess the effect of humidity as variable.

⊕ The researchers have found that *low specific humidity* is a key factor in laboratory transmission of influenza as well as the onset of seasonal influenza in the USA.

⊕ It was reported that *high temperature and relative humidity* reduce the transmission of COVID-19 with 1% significance levels of evidence that *high temperature* and *high humidity* reduce the transmission of influenza.

- This suggested that the arrival of *summer and rainy season* in the *northern hemisphere* can effectively reduce the transmission of the

COVID-19, and it is unlikely that the COVID-19 pandemic diminishes by summer since the central US, northwest China, and countries in the southern hemisphere (e.g. Australia and South Africa) still have a high coronavirus transmission.

Therefore, other measures such as *social distancing* are still important for blocking the COVID-19 transmission.

10. Mass Media's Role in Prevention & Management of COVID-19

The COVID-19 pandemic has created a worldwide challenging emergency that has deeply affected the regular life of every individual and their existence.

- The COVID-19 pandemic is to be known as a more serious public health risk than influenza pandemic of the early twentieth century that killed over 50 million people worldwide.
- The number of infected patients and lethalties of COVID-19 augmenting exponentially and its ultimate global impacts are still mysterious.

- The countries facing novel corona pandemic worldwide have implemented various forms of social distancing to reduce the virus spread until specific medicines and vaccines will be available in the market.

Most of the countries face unique challenges to combat the COVID-19 pandemic.

More specifically, developing countries have:

- Poor healthcare resources,
 - Limited state capacity,
 - A large population below the poverty line, and
 - Monetary issues that are posing a challenge to save life against this pandemic.
- Therefore, countrywide lockdown by keeping in mind the *physical danger*, and *social and physical distancing policy* has forced huge stress on the population below the poverty line.

Meanwhile, the media came in front in qualitative and quantitative means and play a remarkable role in providing the latest updates to people by spreading awareness among them.

- The effect of social distancing are apparent in *India* through data and “*individual-based simulation model*” comparative account with *China, Italy, America, etc.*

- The **data** which have been combined with data on the early and **swift commencement of COVID-19** associated to:

- Demographic pattern,
- Rate of infection and dispersal,
- Frequency of hospitalization with critical care facility, and
- Mortality might be highly influential in the policy arena.

The improvement suggested by Ferguson et al. (2020) in moderate form of social distancing includes:

- A 7-day isolation of anyone suspected with coronavirus symptoms and
- A 14-day entirely voluntary household quarantine to spectacularly reduce social contact is fabulously helpful in lowering *COVID-19* significantly.

All these measures that began in India since late February 2020 may flatten the curve of infection but unable to stop exclusively.

This suppression scenario makes projections for strict and repeated imposition of social distancing throughout the year until a vaccine will be developed for drastic reduction in cases and rebound epidemic.

In every step of this pandemic, **the media always came with the:**

- Latest updates and safety measures,
- Multiple stories,
- Progressive headlines, and
- Politicians' addresses to nation across the past few months.

In any case, this consistent blast of new data, **new cases, and new counsel has been trying to increase awareness.**

It not just makes the story hard to stay aware of from a columnist's viewpoint, it makes it prone to misunderstanding for anybody attempting to follow the story.

A news piece you read one day could be totally obsolete by the following morning, and this has implied that there have been numerous inquiries from the **general society encompassing the flare-up and the infection.**

Furthermore, **as supplementary data** have risen over the previous weeks, specialists and general well-being authorities have reconsidered their **conclusions, exhortation, and proposals** in accordance with this, and it has been **concluded** that **these updates have made it difficult to construct trust.**

11. Influence of COVID-19 on the Economy and Supply Chain

The influence of novel coronavirus disease along with mortality and morbidity has become apparent since the outbreak in highly interconnected global capita.

The worldwide act of lockdown was associated with interruptions to production amidst the slowing down of global economy.

Consecutively, the global supply chain has also been discomfited which leads to **great socioeconomic hike**.

The **discoveries** uncover that the expanding number of lockdown days, fiscal arrangement choices, and travel limitations seriously **influenced the degree of financial growth and the end, opening, most minimal, and most noteworthy stock cost of significant securities exchange records**.

Conversely, the forced limitation on inward development and higher monetary approach spending positively affected the degree of financial growth despite the fact that the expanding number of affirmed coronavirus cases did not significantly affect the degree of financial growth.

Companies worldwide, irrespective of size, have started experiencing reductions in production and export because bounded transport in restricted countries further slowed down global economic exchange activities.

The economic stock markets have also been approachable to changes and global stock indices through **various direct and indirect economic costs** since **novel corona outbreak, disease burden, and associated illness.**

The time, income, and direct financial loss of bearer on medical care and associated services are extra in quantitative asset estimate of the economic loss because of *COVID-19*.

The conformist comes up with underestimation of the **true economic costs of infectious pandemic diseases** for which there is no vaccine until today so far such as:

- *COVID-19,*
- *HIV/AIDS,*
- *Pandemic Influenza.*

The exercises of the earlier reported pandemics might be helpful in the assessment of valuable information for reducing and combating current pandemic outbreak implications.

The **horror and psychological effects of this unknown deadly virus** are **quite more like biological**

terrorism threats which cause a high level of stress, with longer-term consequences.

Social distancing, travel restrictions, and self-isolation not only decrease economic sectors across the world but also caused loss to many educational institutions which have locked down also.

On the contrary, the demand for medical supplies and food resources increases due to panic-buying and stockpiling of medical supplements and food products, which is also a big challenge.

12. To Conclude

In 2002, SARS CoV-1 epidemic created havoc in Guangdong region of *China*, but in December 2019, SARS-Cov-2, novel coronavirus had emerged in *Wuhan, China*, which caused an epidemic in the whole world.

This virus transmitted so quickly that it affected more than hundreds of thousands of people over the world.

Although the source, origin, and transmission mechanism of this virus are not yet clear, there are preventive measures like:

- Social distancing,
- Washing of hands, and

- **Sanitization of hands in public places accepted worldwide.**

Scientists and researchers are rapidly studying on this topic and helping people to overcome this pandemic.

Also, the **doctors, border security officers, army men, police officers, nurses, and municipal workers** are trying their level best to save the world from this disease.

Scientists are hopefully finding and managing an effective vaccine for this virus.

In the meantime, various antiviral drugs mainly in combination with azithromycin were used for short-term benefits.

So, in the end, it is a lesson to be learned on the basis of this viral disaster in terms of global and public health for any future pandemic like this.

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