"A REVIEW ON CORONAVIRUS FAMILY"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfilment of the requirements for the degree of

Bachelor of Pharmacy

BY

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Semester VIII

UNDER THE GUIDANCE OF

DR. SHITAL PANCHAL

INSTITUTE OF PHARMACY

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APRIL 2020

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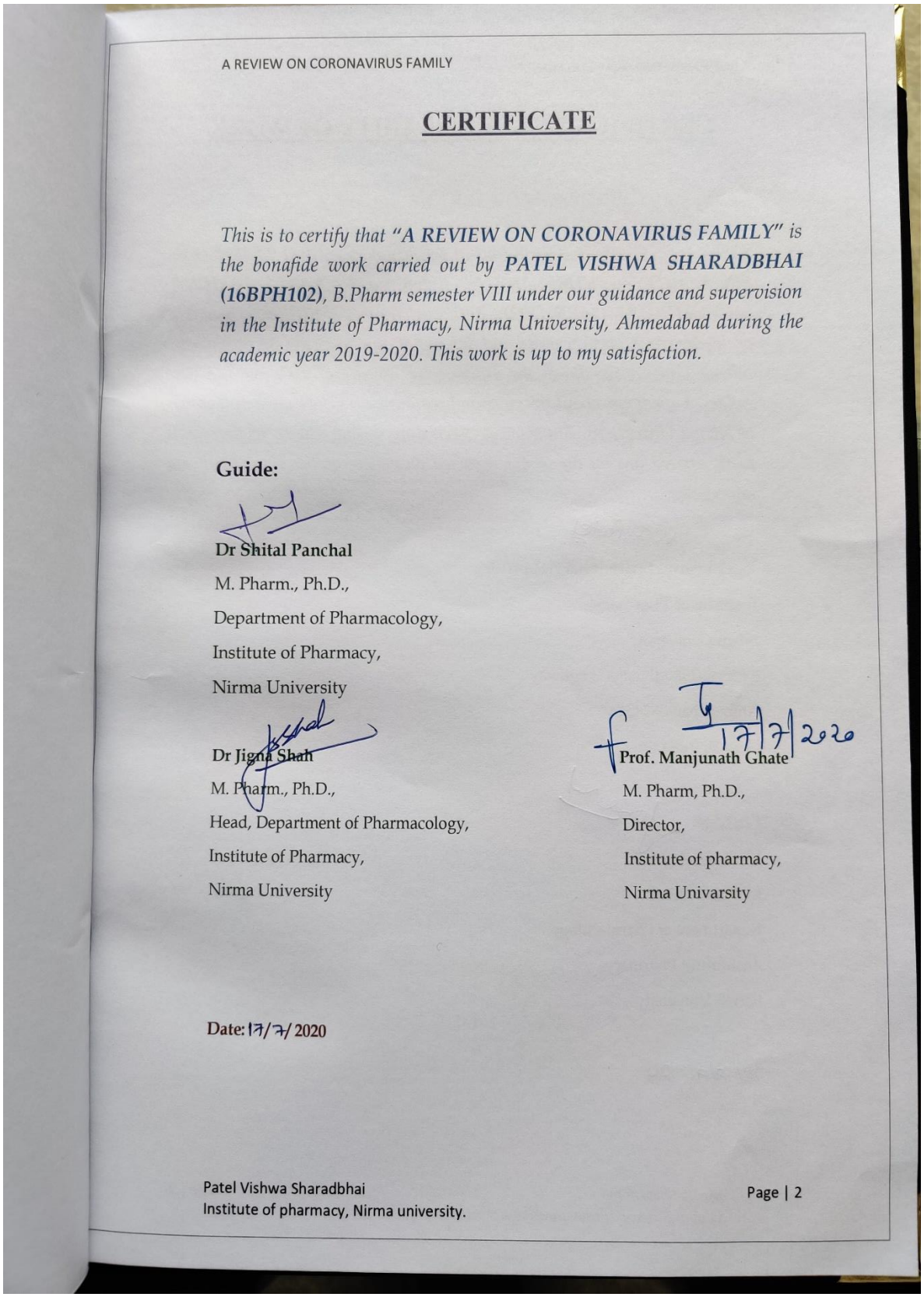

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CERTIFICATE

This is to certify that ***"A REVIEW ON CORONAVIRUS FAMILY"*** *is the bonafide work carried out by* ***PATEL VISHWA SHARADBHAI (16BPH102)****, B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

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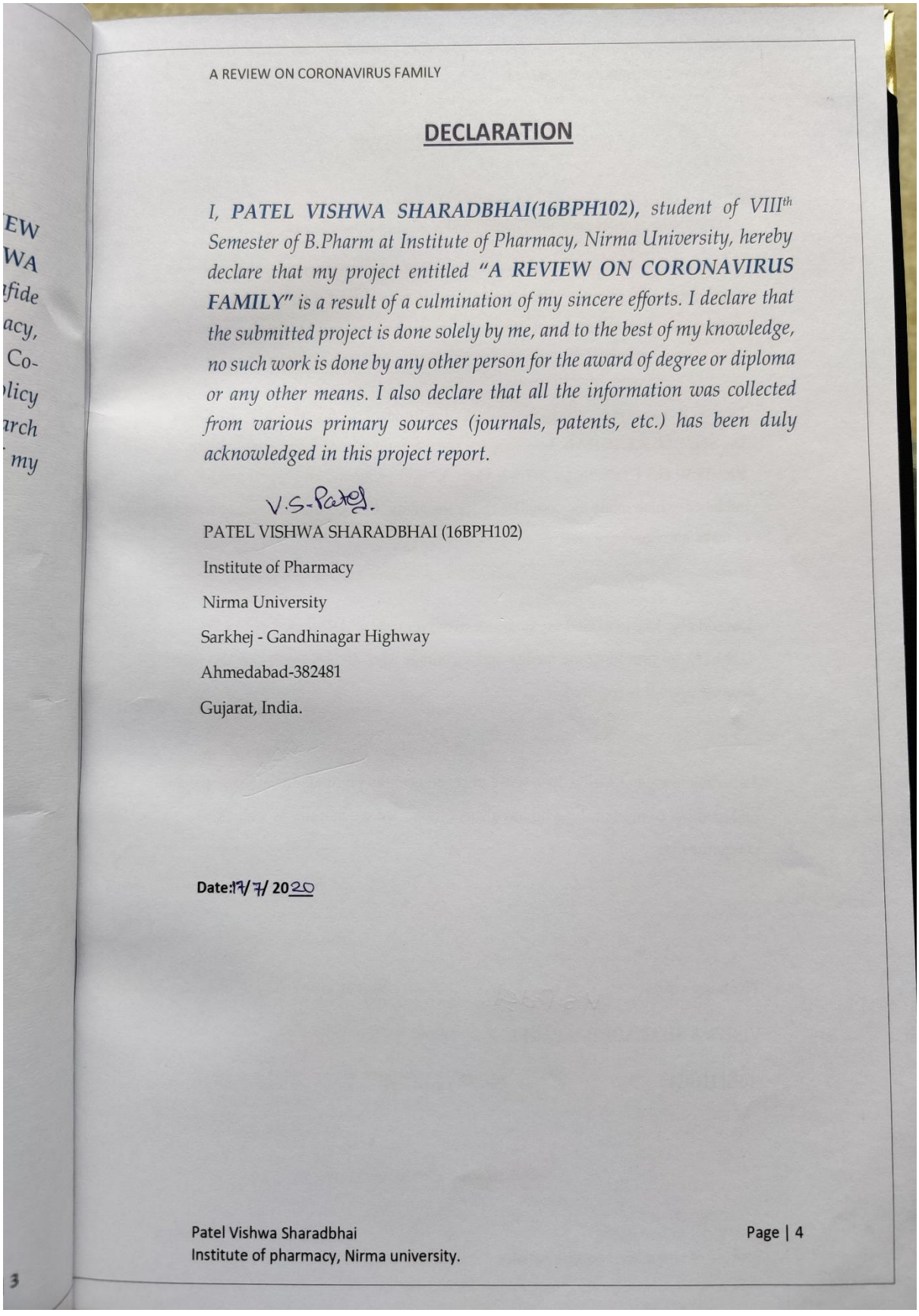

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DECLARATION

*I, **PATEL VISHWA SHARADBHAI(16BPH102),** student of VIII[th] Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"A REVIEW ON CORONAVIRUS FAMILY"** is a result of a culmination of my sincere efforts. I declare that the submitted project is done solely by me, and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*

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Acknowledgement

This project's progress and final result needed a lot of guidance and

Support from a lot of people and I am truly thankful to have all along the completion and achievement of my project review. Everything I accomplished is contributing to such guidance and support and I remember to thank them.

I would like to express my special thanks of gratitudeto my pharmacology professor **Dr. SHITAL PANCHAL** for giving me an opportunity to do the project work in **"A REVIEW ON CORONAVIRUS FAMILY"** and giving me all support and valuable guidance, which made me complete the project duty. I get constant advice and support to make a review very well.

I would also like to extend my gratitude to the director sir **DR. MANJUNATH GHATE,** for providing me facility and encourage us to do new work and also give support when it is required.

I also acknowledge with a deep sense of reverence, my gratitude towards my parents and member of my family, who has always supported me morally as well as economically.

Thanking you, V.S.Patel.

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ABSTRACT

Coronaviruses (CoVs) are considered by cube-alike spikes extending from the external surface. These viruses cover positive-sense RNA viruses.

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These viruses have a remarkably large gene and are a unique approach for replication. In mammals and birds, coronaviruses cause many diseases ranging from the consumption of pigs and cows to upper respiratory tract infections in poultry to human respiratory infections. Such viruses have historically been considered a veterinary concern and have been associated with mild flu in humans. Over the past decade, there has been a high mortality outbreak of COV transmission from animal to male. The extraordinary ability of cross-species transmission is COV exposure to range of cell external surface particles to enter host cells. Here there is delivery a brief overview to corona viruses, describe the basic structure, multiplication, duplication mechanisms & pathogenesis, as well as existing methods for prevention and treatment. We also have an outbreak of the most SARS-coronavirus, MERScoronavirus and SARS-coronavirus-2.

INTRODUCTION

- Coronaviruses are originated in mammalian and avian species. In morphology and chemical composition, they are closely related to each other: for example, human and livestock coronaviruses are associated domestically.

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- Coronaviruses were first recognized by a team of virologists (J. D. Almeida, D. M. Berry, C. H. Cunningham, D. Hamre, M. S. Hofstad, L. Gallasky, K. McIntosh, and D. J. Tyrrell)

PROPERTIES OF THESE VIRUSES

		Avian infectious bronchitis	Mouse hepatitis	Human strains
Size.	Filtration		80–120 mμ	89 mμ
	Electron microscopy*	80–120 mμ	100 mμ	80–160 mμ
Characteristic surface structure		+	+	+
Essential lipid (ether lability)		+	+	+
Apparent ribonucleic acid content (unsusceptibility to DNA inhibitors)		+	+	+
Density of infectious unit		1·18	?	1·19
Replication in cytoplasmic vesicles		+	+	+

* Negative contrast technique—projections are included in the diameter of the particle.

This table explains about details of coronavirus properties.

- However, there is no evidence that animals can transmit human coronaviruses. In animals, different coronaviruses can contaminate a variety of tissues and cause certain diseases, but mild upper respiratory infections, such as persistent colds, are known in humans.
- In rare cases of gastrointestinal coronavirus infection, diarrhea can spread in children
- There are several outbreaks of coronaviruses, together with the extremely pathogenic acute breathing syndrome coronaviruses (SARS-coronavirus), the recognized MERS-coronavirus.
- The current outbreak of severe Acute respiratory syndrome coronavirus - 2 (SARS-coronavirus-2) has been identified & the virus causes COVID-19 disease.

1. CORONAVIRUS AND FAMILY INTRODUCTION:

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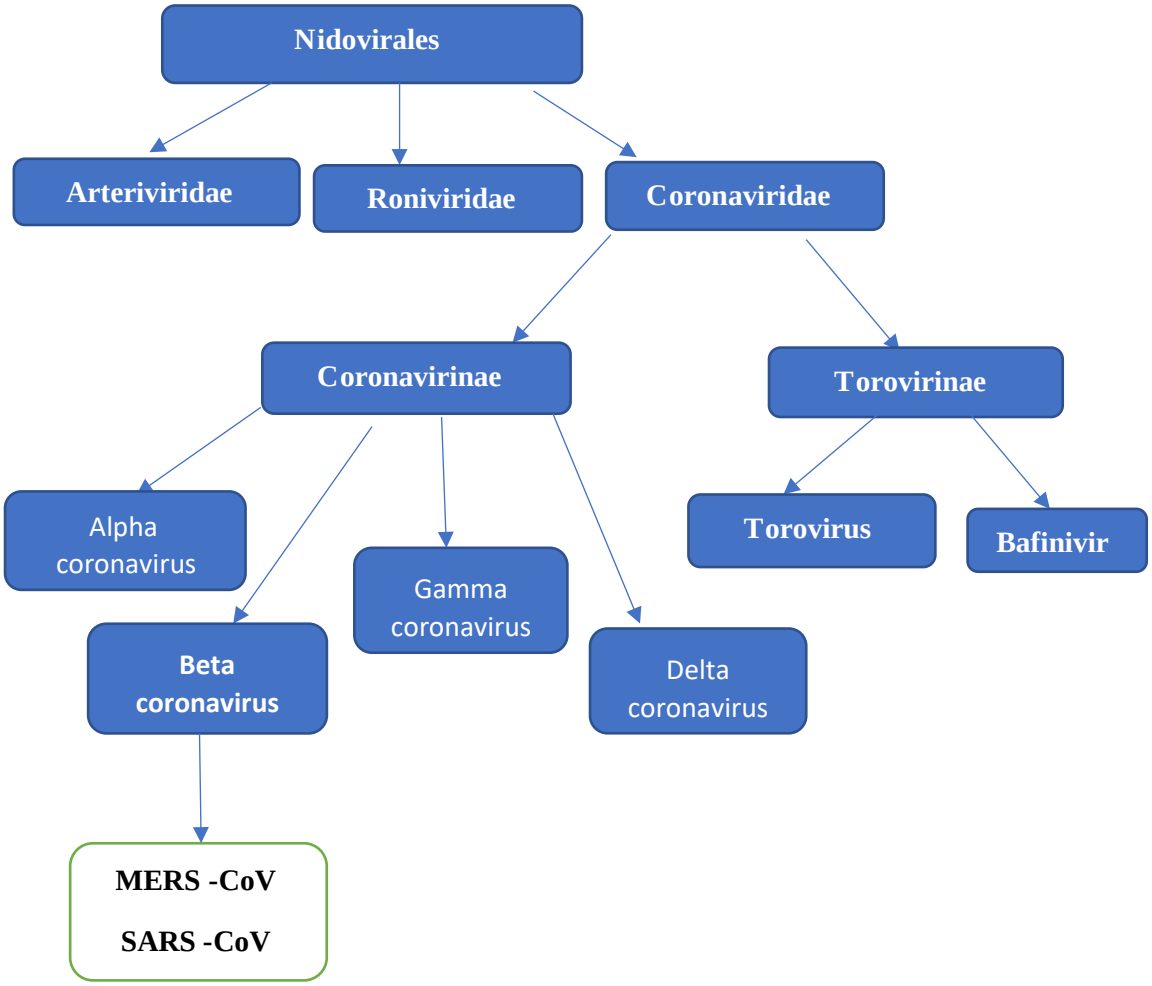

- Coronavirus is the largest group of coronavirus viruses. Nidoviruses are a sequence consisting of arteriosclerosis, ronviridae, and coronaviruses.
- The Coronaviridae family name and subfamily are two subtypes, namely Coronavirinae and Torovirinae.
- coronavirus is divided into four genus:

  alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronaviruses.
- virus was originally organized by serialization in clusters, but is now divided by phylogenetic clustering.
- Beta coronaviruses include MERS-coronavirus and SARS-coronavirus. And the current outbreak of SARS-coronavirus-2 bears similarity to this virus.

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1.1 Classification of disease-causing coronaviruses in humans:

- Alpha-Coronavirus: ○ Human Coronavirus 229E (HCoV-229E)
- Beta-Coronavirus:
  - ○ Human coronavirus HKU1 ○ Human Coronavirus NL63 (HCOV-NL63, New Haven Coronavirus) ○ Human Coronavirus OC43 (HCoV-OC43) ○ Middle East Respiratory Syndrome-Related Coronavirus (MERS-CoV or HCoV-EMC; Causes of MERS)
  - ○ Sever Acute respiratory syndrome coronavirus (SARS-CoV-1, cause of SARS) ○ Sever Acute respiratory syndrome coronavirus 2 (cause of SARS-CoV2, COVID-19)

1.2 Non-human mammals infected with coronavirus:

Animal	Variety of coronavirus
Cattle	Bovine coronavirus (BCV)—severe enteritis in calves
Cats	Feline coronavirus (FCoV)—mild enteritis in cats and severe feline infectious peritonitis
Dogs	Canine coronaviruses (CCoV)—enteritis and respiratory diseases
Ferrets	Ferret enteric coronavirus—epizootic catarrhal enteritis; Ferret systemic coronavirus—a syndrome similar to feline infectious peritonitis
Hedgehogs	Hedgehog coronavirus 1
Mink	Mink coronavirus 1
Pigs	Porcine coronavirus HKU15—gastroenteritis; Porcine epidemic diarrhea virus (PED or PEDV)
Rabbits	Rabbit enteric coronavirus—acute gastrointestinal disease and diarrhea in young European rabbits
Rats	Lucheng Rn rat coronavirus
Whales	Beluga whale coronavirus SW1

1.3 some birds are infected by coronavirus:

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Domestic fowl: Infectious bronchitis virus (IBV)—avian infectious bronchitis
Bulbul coronavirus HKU11
Common moorhen coronavirus HKU21
Munia coronavirus HKU13
Night heron coronavirus HKU19
Turkey coronavirus (TCV)—enteritis
White-eye coronavirus HKU16
Wigeon coronavirus HKU20

1.4 some corona viruses carried by bats:

Bat Hp-betacoronavirus Zhejiang2013
Colacovirus bat coronavirus CDPHE15
Decacovirus bat coronavirus HKU10
Miniopterus bat coronaviruses 1 and HKU8
Pipistrellus bat coronavirus HKU5
Rhinolophus bat coronavirus HKU2
Rhinolophus ferrumequinum bat coronavirus HuB-2013
Rousettus bat coronaviruses GCCDC1 and HKU
Scotophilus bat coronavirus 512
Tylonycteris bat coronavirus HKU4

2. History of coronavirus :

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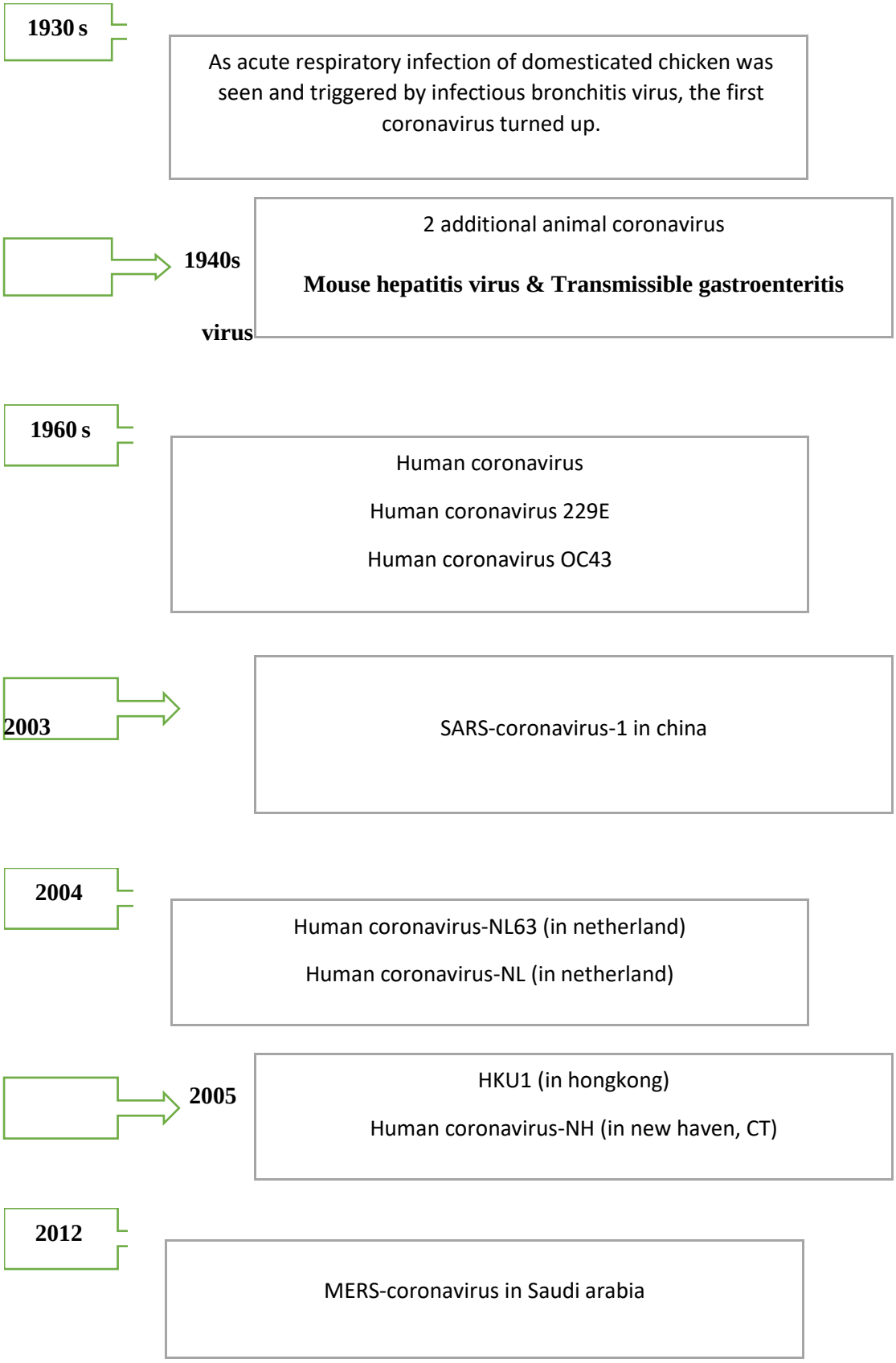

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2019

SARS-coronavirus-2 in china

- In 1965 , Human coronavirus 229E is now known as common cold. This is the first human coronavirus. And OC-43 also causes colds.
- In 2004 , NL-63 coronavirus causes the mild or moderate upper respiratory tract contaminations and more infections to the lower part of the respiratory tract. ○ In 2005 , HKU1 coronavirus causes the respiratory tract infection.

3. SUBFAMILY CORONAVIRINAE:

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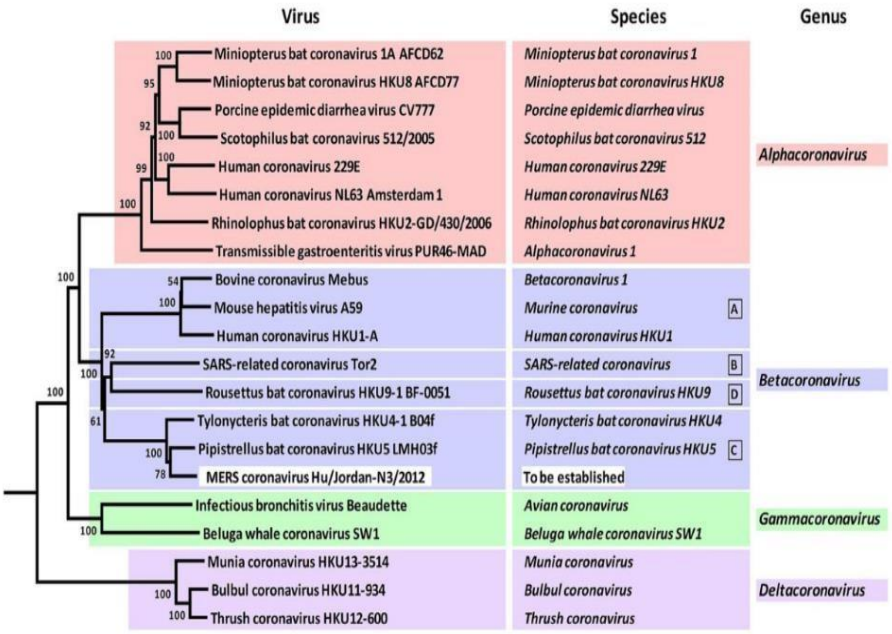

Figure:3.1 This chart describes the names, species, and strain of the subfamily coronavirinae virus.

- The Viral Taxonomic Convention identifies the genetically modified COV strains with delta-cove, the newest member of the three accepted species, alpha-, beta-, and gamma-COV.
- Figure In this figure, the inactive neighbour-joining tree constructed from coronaviridae-wide-amino alignments conserves the domain of polycrotein replication 1ab in 21 COVs.
- To each of these is a illustrative of the presently known COV species.

3.1 alpha genus :

- ✦ The COV in this gene exhibits a characteristic cleavage characteristic of its replication polyprotein, Nsp1, which differs in sequence and size from betacoronavirus, and the relative lack in candidates in gamma-COV.
- ✦ They display a widely shared attachment of gene for the CoV dispensable alpha-CoV -specific membrane protein (αmp), which contains only 6 affinity genes identified for some members, and 6 associated genes for some members, including canine members. Go.
- ✦ The Alpha-Cov is a cluster of important animal and human viruses that are divided into numerous species.

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- Human coronavirus, HCoV-229E and HCoV-NL63, and other members of the alpha species include porcine epidemic diarrhoea virus (PEDV) and some bat coronavirus.
- All mammals are animals that are hunted by a specific alpha-coronavirus.
- Humans (HCoV-229E & HCoV-NL63),
- Cats (Feline CoV: Type I & Type II),
- Dogs (Dogs CoV: Type I & Type II),
- Pigs (TGEV, PRCV, PEDV) & Bats, ✦ These Viruses are included in genus.

3.1.1 ***TGEV:*** This is the most considered coronavirus of Alpha-coronavirus strain. This virus with diarrhoea and dehydration mainly affects the intestinal tract, but can also cause fewer respiratory infections, resulting in 90 percent mortality in newborn piglets.

3.1.2 ***HCoV-229E:*** The first human coronavirus (half of the 1960s), identified as mild human cold or pneumonia in immunocompromised patients with HCoV-OC43 (beta-coronavirus). Which is related to the alpha-coronavirus. HCoV-NL63 causes high inflammation of the lower part of respiratory tract, and bronchiolitis, but usages a different receptor for penetration.

3.1.3 ***PEDV:*** It was firstly detected in Europe. It has become even more troublesome in countries of asia, and with the invention of its latest breed, American Reiss, vaccines (developed in previous variants) have been partially transformed into a safer spike. In piglets, PEDV results for the cause of excessive diarrhoea and dehydration. It has a different tropics to Tgev and does not kill cells, which is the most sensitive cell line to TGEV.

3.2 beta genus:

- The gene has a different NSPI sequence of coronavirus than the alphacoronavirus1 and includes four different line species. ○ A : (MHV, HCoV-

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HKU1 and Beta-CoV1), ○ B : (SARS-CoV), ○ C : (HKU4, HKU5 and MERS-CoV), ○ D : (HKU9).

- HCoV-OC43 and SARS-CoV, and newly developing MERS-coronavirus are the most representative versions of this class. CoV shelter like Glycoprotein, Her Majesty, extra short shot.

3.2.1 ***HCoV-OC43:*** This virus can cause chronic and severe colds and pneumonia in patients with HIV infection, such as chemotherapy and / or immunosuppressed patients. It occurs in 4 genotypes: a, b, c, and d , in which d is triggered over time by natural recombination.

3.2.2 ***MHV:*** This species is the best observed and studied the beta-COV before SARS-coronavirus is developed specifically in vivo and in vitro laboratory mouse. Many strains induce inflammation to many rat tissues, such as the JHM and A59 neurotrophic strains that cause acute encephalitis and chronic discharge of the survivor, which later serves as a example for multiple sclerosis studies. adaptive and innate immunity are important for the host resistance.

3.2.3 ***SARS-CoV:*** : The virus has recorded a malignancy rate of 9.6 percent (WHO, 2004), spreading worldwide to the attention of scientific groups on coronovirus. SARS begins with flu-like symptoms with more than 100 fevers, followed by breathlessness and pneumonia. For some major depressive disorders, chronic symptoms include pulmonary fibrosis, osteoporosis, thigh necrosis and so on. This is far more harmful than the immune system's reactions to the so-called

"cytokine storm."

3.2.4 ***MERS-CoV***: This virus is also known as CoV-EMC because it was the first isolated human at Erasmus Medical Center, a decade after the SARS pandemic, a human coronavirus that originated in Saudi Arabia in 2012. As of May 2014, MERS reported 700 deaths from 20 countries. Beta-Cove shares 90% of the sequence identity docked in line 2c with Bat-Cove HKU4 and HKU5.

3.3 gamma genus:

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- The NspI fragments in Alpha and Beta-Cove do not usually include this class. IBV infects chickens and was the first Cove to exhibit the most contagious CoV infections in eggs in the 1930s, affecting enteric, respiratory, renal and reproductive systems.

4. STRUCTURE OF CORONAVIRUSES:

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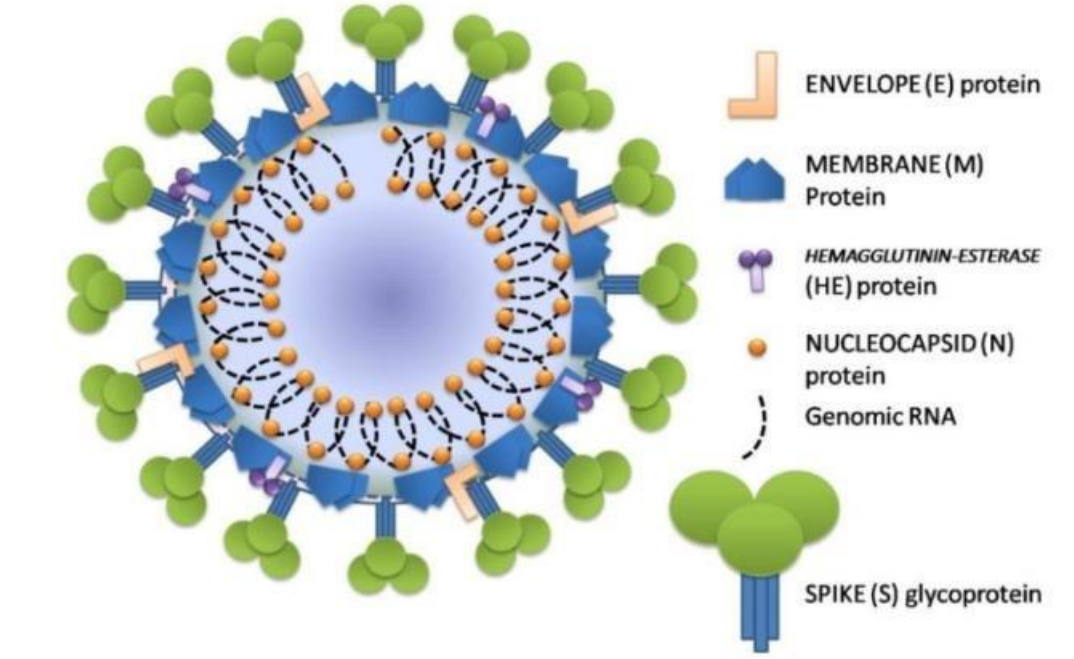

Figure: 4.1 diagram describing morphology Characteristics of the virus cell

4.1 general structure of coronavirus:

- coronaviruses are single-stranded RNA viruses. These have a diameter of approximately 120 nm.
- They are prone to mutation - recombination and they are more complex.
- There are around 40 distinct species, and they mostly infect birds, both human and non-human mammals.
- Coronavirus exists in bats and wild birds.
- They are capable of spreading to other species and therefore humans.
- The virus is named corona because the corona means 'crown' and the virus looks like a crown structure. This crown like structure comes from its spikey glycoproteins or pelopomers

4.2 spike protein (S) :

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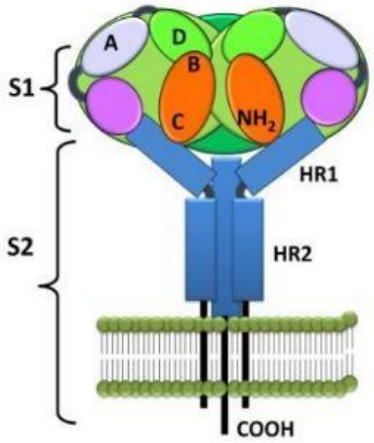
- ✦ The envelope has the cube-shaped glycoprotein projection.
- ✦ This spike glycoprotein helps viruses enter the host cells. ✦ These spikes have two subunits;

Figure.:4.2 protein spike

1. **S1** : This subunit attaches to the receptors on the surface of host cells. Spike subunit binds with ACE-2 enzyme to the external surface of the S1 cell membrane. The host transmitter serum protease, TMPRSS2, then stimulates the spike & clears ACE-2 enzyme.
2. **S2:** This subunit joins the cell membrane. Protease also works on the S2, which facilitates combination of cell membrane. virus finally enters into cell.



4.3 Membrane protein (M) :

- ✦ protein in this layer is type 3 glycoprotein.
- ✦ It contains a long C-terminal domain that encloses inner layer leaflet forming lattice thick like matrix that describes the abnormal thickness of the coronavirus cover.
- ✦ Important roles in assembly of virus, such as RNA genomic package to the capsid of nucleus ascending membrane protein.

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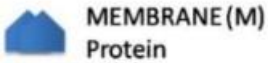
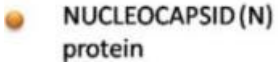


4.4 Envelope protein (E):

- This protein is a small 8.4 to 12 kda, inner cell membrane protein forms pentamers and it has cation-selective ion channel movement.
- It is essential in virus assembly and morphogenesis.
- It is a virulence factor in SARS-coronavirus.

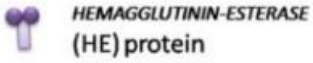
4.5 Nucleocapsid protein (N) :

- Nucleocapsid protein has 50–60kD, which is responsible for RNA binding phosphoprotein genome encapsulation, exhibits synthesis of RNA, translation of RNA amperon activity and acts like an interferons antagonist.



4.6 hemagglutinin esterase protein (HE) :

- it is a small spike as glycoprotein initiate only in Beta-coronavirus gene lineage & interacts with sialic acid in MHV.
- Sequence coronavirus HE proteins are divided 30% amino acid sequence with resemblance to influenza c.
- HE protein helps in the early absorption of COV into the layer of hostcell, but it does not initiate contamination in the nonappearance of spike proteins.



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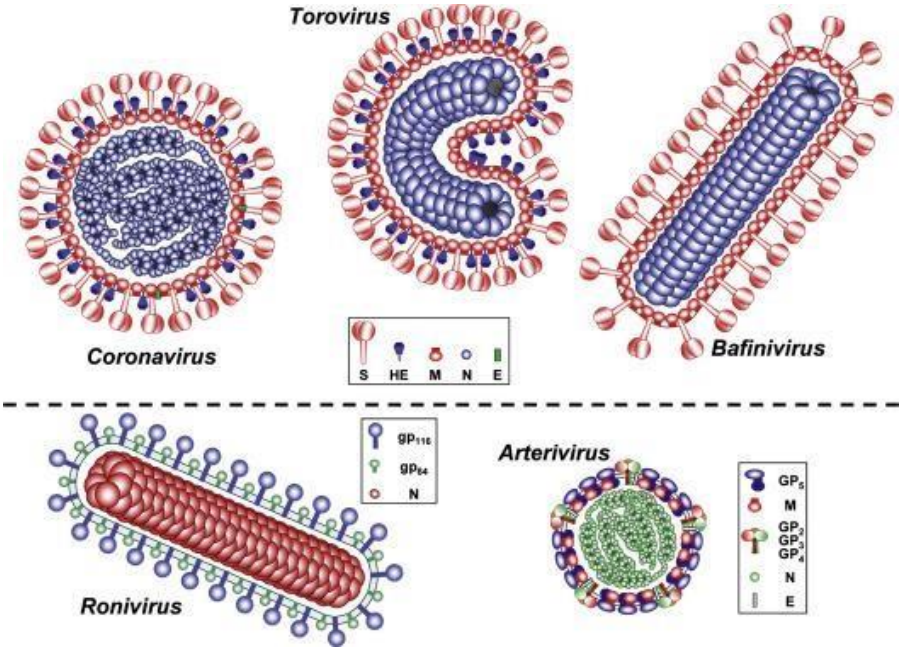

This figure have all the structure of full family of coronavirus.

5 MECHANISM OF CORONAVIRUS:

5.1 Multiplication :

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- Human coronavirus enters host cells mainly through specific different receptors. For 229E & OC43, respectively, the receptor containing aminopeptidase-N and sialic acid.
- The gene is transmitted and transmitted after virus enters and uncoats to host cell.
- A unique and different feature of replication is, mRNAs are normal 3; Create a "group set" with loops; The translation of the 5 parts special parts only ends.

Seven mRNAs are produced.

- The minimal mRNA codes for nucleoproteins and others dictate the synthesis of another section of each gene.
- Proteins converge in the cell membrane and the gene cell is released from the inner cell membrane to form mature cell forms.

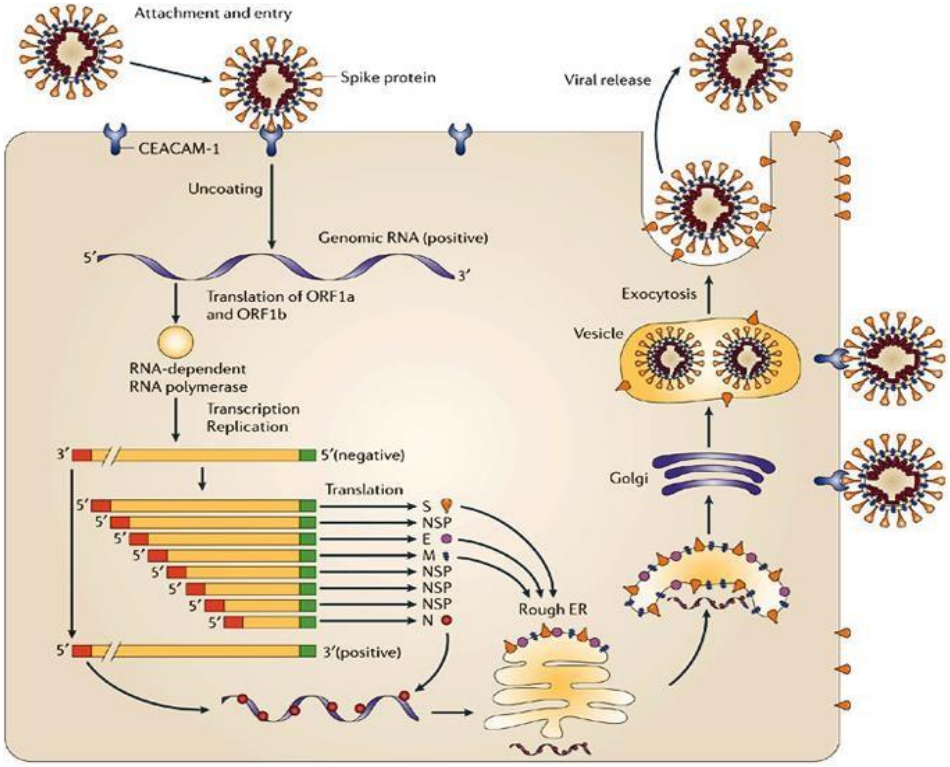

Figure.: 5.1 This figure displays the mechanism of multiplication or replication of coronavirus.

5.2 How the coronavirus enters in the host cell:

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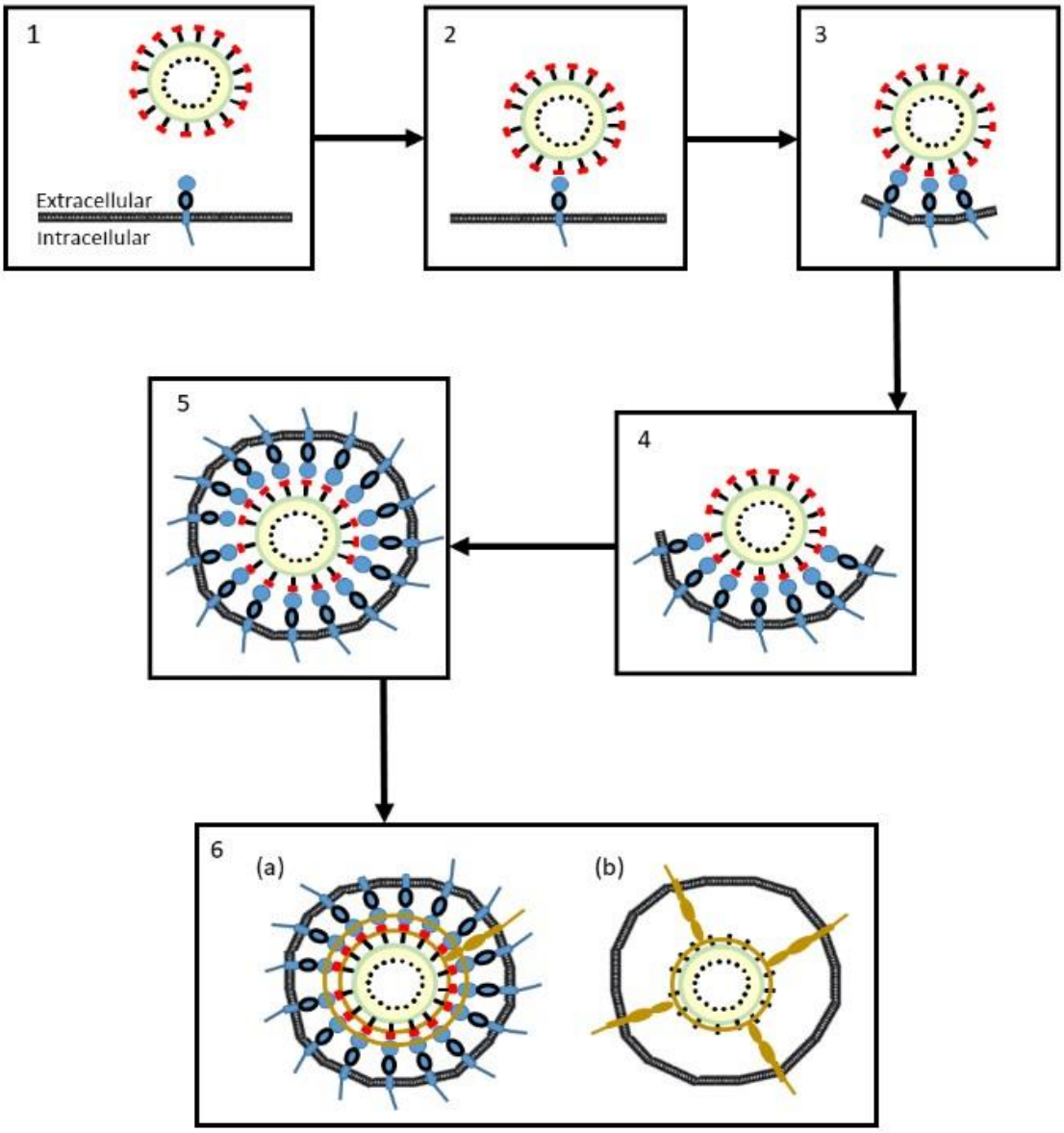

Common Steps for entering coronavirus in host cells

1. The virus reaches the cell membrane.

2. Here is a red ; S1- subunit located at end of the spike protein of the virus. The S1 subunit attaches to the membrane-bound molecule of the specific receptor. Here is a blue specific receptor.

3. Excess glycoprotein spikes when the S1 subunits connect to the membrane-bound receptor begin to make an envelope to the outer membrane virus which is called an endosome.

4. Then progression continues at this stage.

5. This process stops when the endosome is fully prepared.

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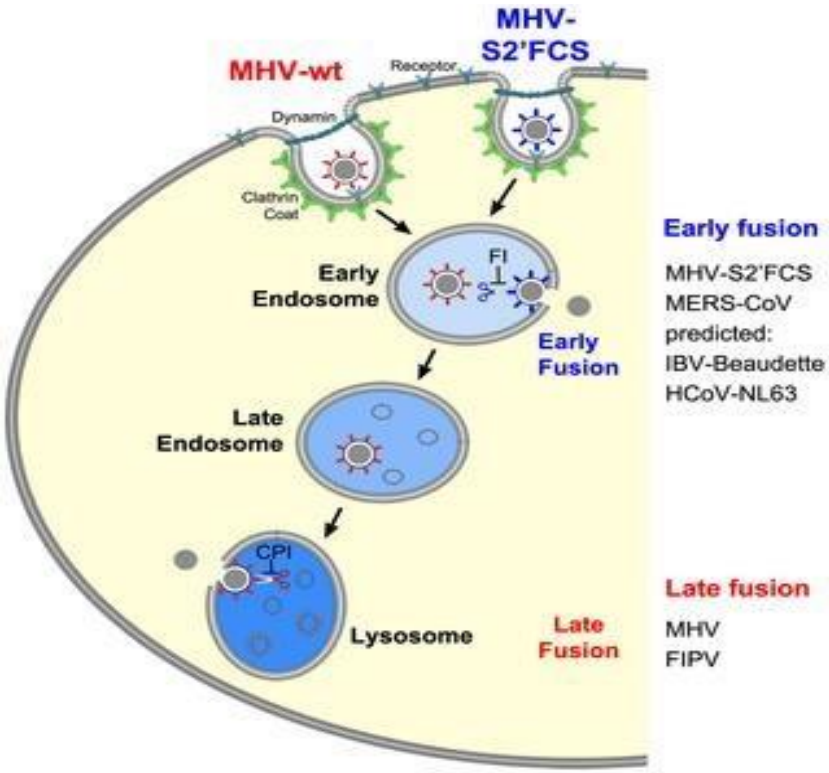
6. Here the virus enters the cell in two different ways:

a. protease which is the cell membrane bound, which is brown in colour in figure, disappears the S1-subunits as of its S2-subunits & also clears enzyme or receptor; The endosome enters in the host cells (this process is called as endocytosis) , where virus is free by the acidification or thyresis of protease.

b. same protease results as a cause of irreversible changes in the S2 subunit of the virus, activates them, and then the virus enters into cell membrane and is infected by the cell.



6 CORONAVIRUS GENOME ORGANIZATION:

- The coronavirus RNA gene is infectious, undifferentiated, single-stranded and 5 "capped and 3" polyadenylated, like most eukaryotes.
- In Figure 6, the RNA gene starts at the 5'end, which contains the leader RNA, followed by the 5 UTR, followed by 2-overlapping ORFs, which is 1A & 1B, & 60%-of genes.

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- These encodes for polyproteins(rep1a and rep1b) with process of ribosomal frameshifting, which is processed on non-structural proteins, viral RNA-based RNA polymerases (RDRs) For, mainly) protease (Mpro).
- Gen 5 "-SEMN-3", expressed from subgenomic mRNAs from the category of 3'-cotterminal packages, constitutes non-structural CoV genes. (Figure 6.2)
- Among structural genes, at least eight associated genes are interrelated, which are required for the natural infection but not in form of in vitro.
- there is the signal for polyadenylation after 3 "UTR (200-500nt). UTR shares gene replication and encapsulation signals with adjacent and internal coding regions.

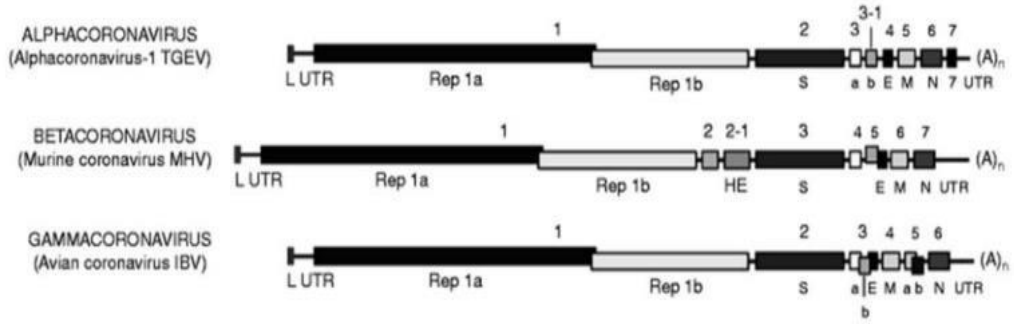

Figure: 6 Genomic distribution of the coronavirus prototypes respective to three genera.

7 CORONAVIRUS INFECTION CYCLE:

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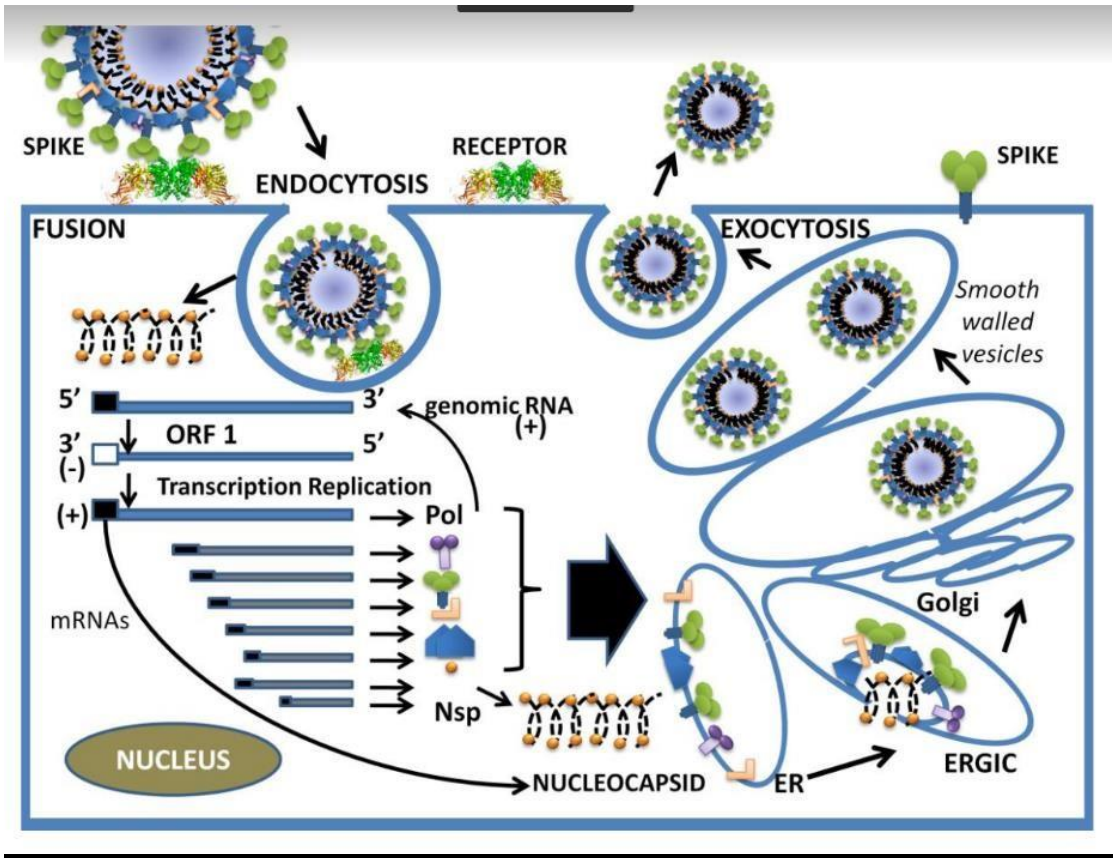

Figure.:7.1 The coronavirus infection lifecycle

7.1 attachment and entry:

- In the first stage of infection, the coronavirus S1 subunit is attached to the spike glycoprotein and the host cell's receptor.
- After all spike proteins are coupled to receptors, endocytosis occurs.
- After this combination and endocytosis, the coronaviruses enter the host cells.

7.2 replicase protein expression:

- Transcription of replication genes from viral genomic RNA is the next stage of the coronavirus life cycle.
- The replication gene contains 2 large ORFs (rep1a and rep1b), that promote 2 co-terminal polyproteins(pp1a and pp1ab).

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- To promote both polyproteins, the virus uses the slipping sequence of 5 to UUUAAAC-3 & RNA pseudocode, which causes the ribosomal shifting of frame from the rib1b frame reading in rep1b ORF.

7.3 replication - transcription:

- RNA synthesis of virus cell involves translation & synthesis of complexes associated with replication of virus cell.
- viral RNA synthesis produces genomic and subgenomic RNA. Subgenomic RNA serve as mRNAs for the structure and associated gene that exist in under polyprotein replication.
- Coronaviruses are also known for recombination using homologous and nonhomologous recombinations.
- The recombination ability of these viruses is linked to the element converting capability of Rd-Rp protein.

7.4 assembly and release:

- Translation of viral structural proteins spike protein, envelope protein and membrane protein, & induction of RNA into endoplasmic reticulum-(ER) after replication and sub-gene combination.
- proteins go through secretion path to the ER-golgi mid – section.
- This leads to the development of large, multi-nuclear cells that allow the virus to spread or neutralize in a specific organism without virus-specific antibodies.

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8 MERS-coronavirus:

- Middle East Respiratory Syndrome disease is a viral respiratory disease caused by coronavirus (MERS V CoV)in Saudi Arabia, 2012.
- MERS 35% of patients died of MERS-CoV infection.
- According to current scientific evidence, Dromedical camels are the main receiver host for MERS-coronavirus & then by an animal cause of MERS infection spread or infect in people.

8.1 Symptoms & Complications:

• Symptoms begin to appear 5 or 6 days after infection. But it also lasts about 2 to 14 days.

8.1.1 symptoms:

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- Many people are reported to be infected with MERS-CoV, which is a serious respiratory illness: ○ Fever ○ Breath shortness ○ Cough
- Some people felt symptoms of diarrhoea and nausea.

8.1.2 complications:

- Many individuals with MERS have many serious health problems, for example pneumonia and kidney failure.
- Out of every 10 people testified with 10 MERS-virus, 3 or 4 died.
- Most individuals who die have a pre-existing medical condition that impairs their immunity, or an underlying health disorder that has not yet been identified.
- Pre-existing conditions in MERS-infected persons, ○ Diabetes ○ Cancer

○ Chronic diseases which are related to heart, obstructive pulmonary, kidney.

- Some infected people have little or no symptoms (such as colds).

8.2 Transmission:

- ✦ When an infected person coughs, MERS coronavirus spreads through respiratory secretions.
- ✦ MERS-coronavirus can spread from illness to others individuals over close communication with the ERS to look after or live with an infected person.
- ✦ Patients infected in the medical care environment, including hospitals, transmitted MERS-CoV to others.
- ✦ Experts investigating ER MERS have not observed a persistent prevalence of MERS-CoV in the population.
- ✦ Recently, after a close relationship with an infected individual who travelled from the arabian countries, some MERS got infected.

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8.3 Prevention & Treatment:

8.3.1 Prevention:

✦ These prevention points were taken during the MERS-CoV outbreak.and these prevention are same as sars outbreak and general hygiene prevention.

8.3.2 treatment:

- ✦ First, patients must be hydrated.
- ✦ Antipyretics and analgesic medicine are given away.
- ✦ Other medical treatments include supportive therapy for infected patients.
- ✦ Antibiotics are given to treat a bacterial infection if there is a bacterial superinfection.

8.4 laboratory tests:

- ✦ The CDC works with public health departments at the state and local level to identify and monitor travel industry partners and others who are contaminated with MERS-CoV.
- ✦ CDC performs several specialized laboratory tests to detect MERS-CoV infection.
- ✦ There is two laboratory tests,

A. **Molecular tests:** It detects active infection.

B. **Serology tests:** detection of previous infections by detection of antibodies to MERS-CoV. Serology tests are targeted for observation or research purposes and not for clinical purposes.

8.5 structure of MERS-CoV:

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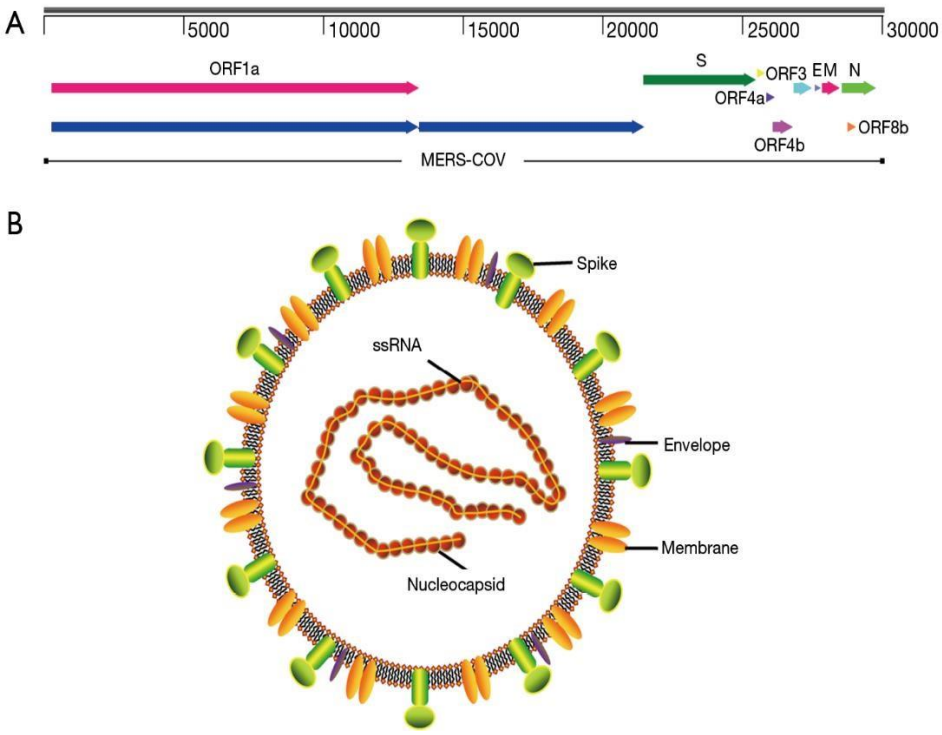

Figure.:8.5 structure and genome of MERS-CoV

- The MERS-CoV gene has 5-terminal structure with polytail at the finish part of genome, recombining the without gene protein, which contains two-thirds genes at the 5' finish part of the gene, which are 16 non-structural proteins are included.
- 4 structural proteins, including spike (S), envelope (E), membrane protein (M) and nucleocapside (N), and 5 proteins in the appendix.
- MERS-coronavirus gene was normally organized in the organization of the 5'terminal-ORF1a-ORF1b-S-E-M-N-3 'terminal, and the secondary proteins are simultaneously bound by structural genes.
- Viral membranes contain S, E and M proteins and the spike protein plays important roles in viral production.
- MERS-coronavirus binds human protein-cell receptor to depeptidyl peptidase 4 via the spike protein receptor binding domain (RBD).
- Proteins **M** & **E** play significant roles in **assembly of virus**.
- **N** protein is necessary for **synthesis of RNA**.

8.6 vaccine and antiviral developments related to MERS Disease:

8.6.1 vaccine:

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- Vaccine & successful anti-viral therapy against MERS-coronavirus infection have not been identified.
- The MERS-CoV spike protein, which is reason for er MERS-coronavirus entry, is known as the primary development of vaccine target against MERScoronavirus infection.
- Several vaccine individuals have been developed that target S proteins, including V vaccine vaccines, subunit vaccines, and recombinant vector vaccines.
- In mice, vaccines of DNA uttering the MERS-coronavirus S1 subunit induce anti-gen-exact humor and cellular immune replies.
- Furthermore, the RBD component induced a high IgG antibody in mice to compared to other S protein regions.
- In mice, recombinant carriers expressing the MER-COV S glycoprotein have shown immunity.
- There are fewer studies on the protect function of virus specific CD4 T cells, particularly in respiratory coronavirus infections.

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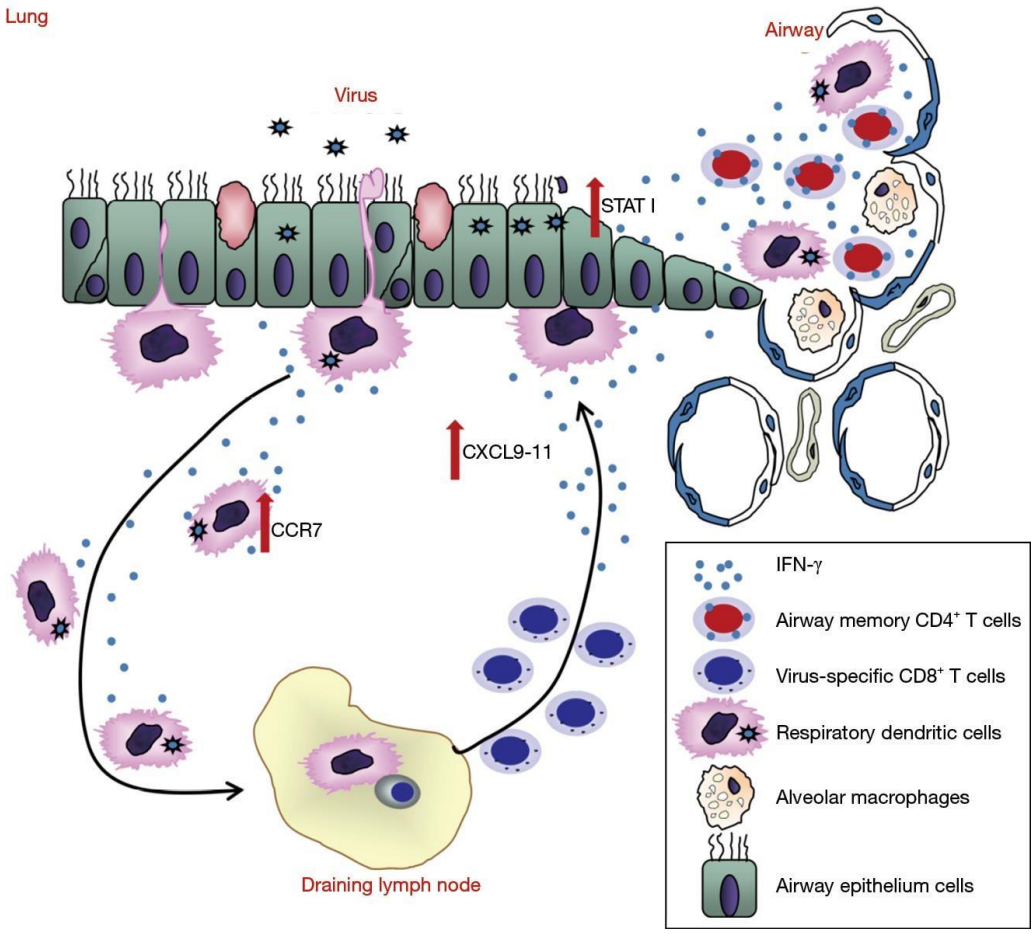

Figure.:8.6.1 Air route memory CD4+ T cells intermediate protective immunity

- Cells These cells enhance the regulatory anti-viral natural response early in contagion and facilitate CD8 T cell-response by mobilizing RDC migration and CD8 T-cells.
- The combination of CD4T memory cells and CD8T memory cells, which can produce neutralizing antibodies, provides enhanced protection against MERScoronavirus and other respiratory infections.
- Most importantly, these CD4T cells respond to many other COVs by targeting the conserved N protein cross-epitope, suggesting that CD4T stimulation to airway memory-cells should be measured part to any worldwide human coronavirus vaccine.

8.6.2 Antiviral drugs development:

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- Human monoclonal antibodies can be used for immune and post-revelation or exposure therapies.
- Deactivating monoclonal antibodies binds with the MERS-CoV spike protein, prevents entry of virus, subsequent fusion of membrane, thus preventing replication of virus and reducing disease to human and animal.
- Several effective monoclonal antibodies have been established from infected MERS patients, monitoring mouse monoclonal antibodies to MERS receptor binding domains or human antibody FAZ libraries.
- These monoclonal antibodies target the spike protein receptor ligand domain region.
- Furthermore, numerous antiviral drugs have been established, with the peptide fusion inhibitor, a small molecular entry stimulant targeting the region of S2, which targets S, Interferon-β, IFN-Δ and ribavirin. Keeping up.

Medication[a]	Normal renal function (CrCl > 50 mL/min)	Impaired renal function[b] (CrCl 20-50 mL/min)	Hemodialysis or CrCl < 20 mL/min
A. Ribavirin, high dose[c]	2,000 mg po loading dose → 1,200 mg po q8h for 4 days → 600 mg po q8h for 4-6 days	2,000 mg po loading dose → 600 mg po q8h for 4 days → 200 mg po q8h for 4-6 days	2,000 mg po loading dose → 200 mg po q6h for 4 days → 200 mg po q12h for 4-6 days
Ribavirin, alternative intermediate dose[d]	2,000 mg po loading dose → 10 mg/kg po q8h for 10 days	2,000 mg po loading dose → 200 mg po q8h for 10 days	2,000 mg po loading dose → 200 mg po q12h for 10 days[e]
B. Interferon-α2a[f]	180 μg per week for 2 weeks	Same dose	Same dose
C. Lopinavir/ritonavir[g]	Lopinavir/ritonavir 400 mg/ 100 mg po q12h for 10 days	Same dose	Same dose
D. Convalescent plasma	300-500 mL of full plasma (3-5 mL/kg)		

[a] In the case of adverse effects caused by ribavirin, the dose should be reduced or its use should be suspended.

Figure.: 8.6.2 list of antiviral drugs to treat the MERS-CoV

8.6.3 Therapeutic Algorithm of MERS-CoV:

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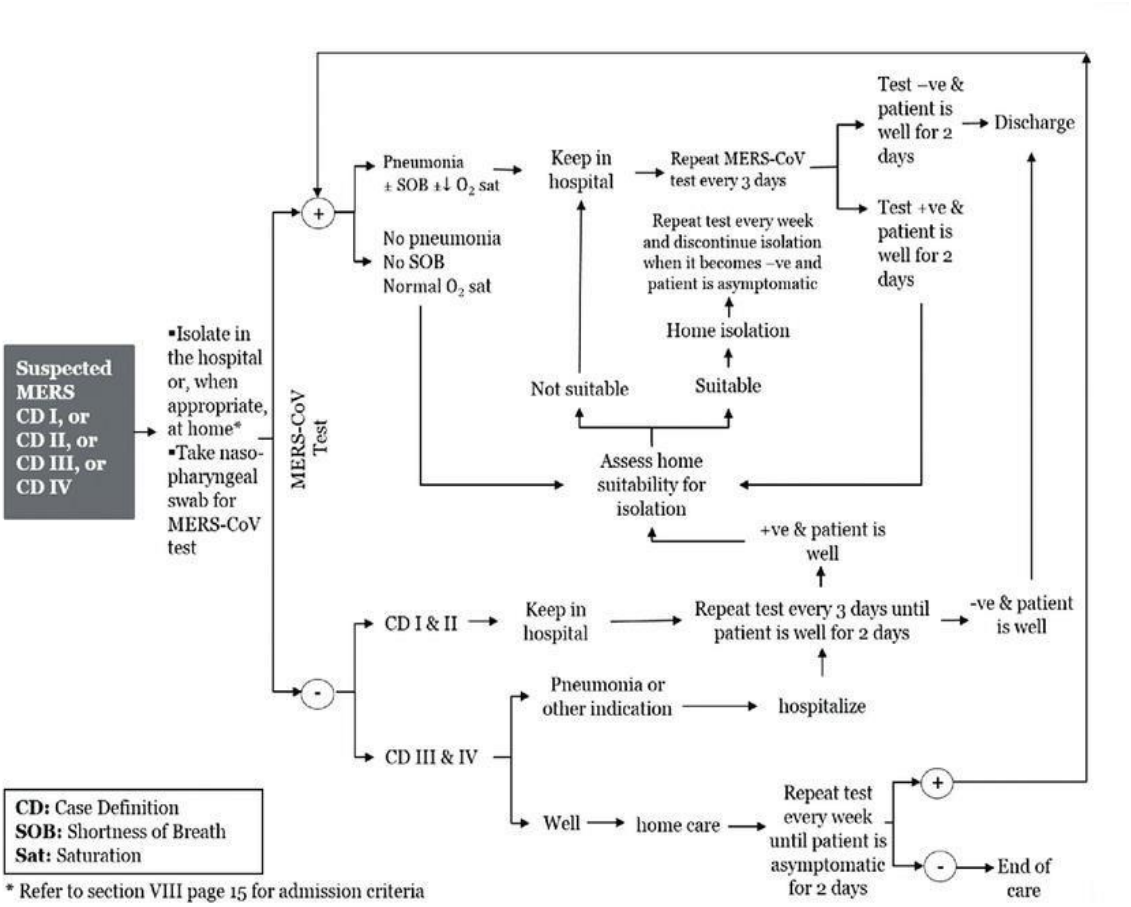

9. SARS-coronavirus:

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- SARS-coronavirus first appeared in human population in November 2002.
- SARS-CoV Animal Isolate Studies have shown that the virus originates mostly from bats, which first spread to humans in Palm Civet and eventually to the wet markets of South China.
- The outbreak reported approximately 8500 cases, with a fatal rate of at least 10%. SARS-CoV circulation is not currently recorded.
- The SARS-CoV outbreak acts as an important part in workers of health care & patients in the hospital.
- SARS-coronavirus has been known as a human pathogen that is phylogenetically different from the two human pathogens Coronavirus 229E and OC43, the first causing mild upper respiratory infections and more severe influenza-like illness in children and the elderly. Said.
- The SARS pandemic affected 26 countries and in 2003, over 8000 cases occurred.
- Since then, a limited no. of cases have been caused by laboratory events or, perhaps, human transmission from animals (Guangdong, China).

9.1 Symptoms:

- In SARS-CoV infection, symptoms are like influenza.
- Another of the following features, ○ Fever ○ Illness ○ Myalgia ○ Headache ○ Diarrhea ○ Shiver
- No individual signs or group of symptoms have been shown to be specifically diagnosed with SARS.
- Here, fever is a common and frequent symptom of infection. It is sometimes missing from the initial measurements, especially in the elderly and immunocompromised patients.
- Symptoms of the second week; ○ Cough (usually dry) ○ Shortness of breath ○ diarrhea

9.2 Transmission:

- SARS-coronavirus has also been spread from person to person.
- It appears to occur mainly in the second week of infection, with respiratory secretions and virus secretion in the feces reaching a peak, and when reports of serious illness begin to decline clinically.

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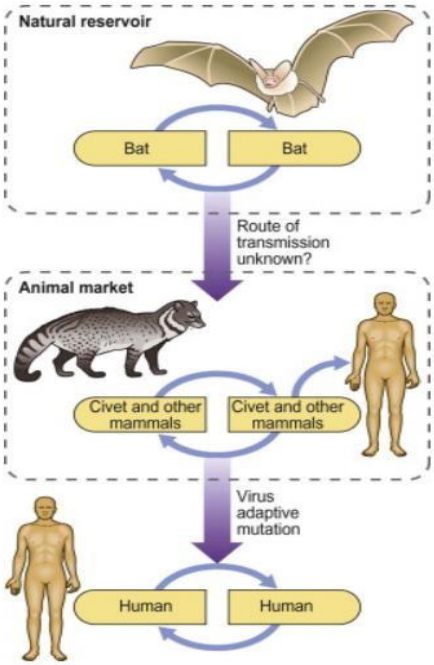

Figure.:9.2 transmission flowchart

- SARS-CoV is mainly transmitted by droplet transmission, while foamytes and feces are also possible modes of human transmission.
- There have been many reports that human health has been transmitted to the environment in the absence of adequate infection control measures.
- The introduction of effective infection control methods has brought an end to the global epidemic.

9.3 ***causes:***

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- SARS-Coronavirus results as a cause of a typical pneumonia that is speedily spreading all over the Asia countries, North America country and European aountries between 2002-2003.
- Infection of sars-coronavirus causes bronchial epithelial cell peeling, damage of cilia, multicellular huge cells, alveolar interstitial fiber cell hyperplasia and fibrocystic disease of lung.

9.4 structure of SARS-CoV:

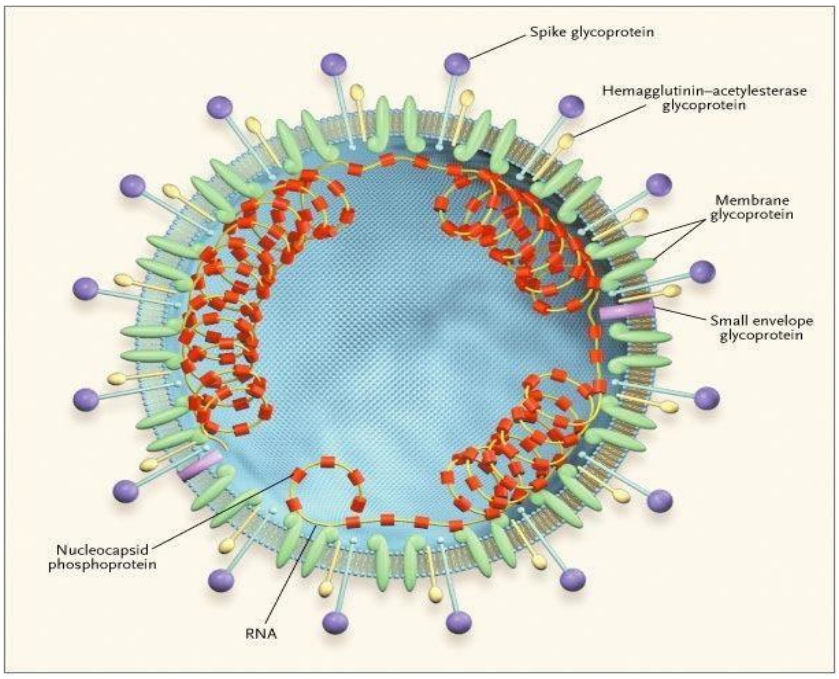

Figure.:9.4 diagram of sars coronavirus

- SARS-coronavirus has the protein structure similar to the three previously identified coronavirus groups: ○ spike glycoprotein (s) ○ protein of membrane (M) ○ Protein of envelope(E) ○ Nucleocapsid protein (N).
- Synthesis of corona virus RNA requires coronavirus N protein and has RNA capacrone functionality that can participate in template switches.
- Spike glycoprotein 1255 long amino acids, limited protein acid supplementation (20–27%) in other coronaviruses.

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- Its carboxyl terminus contains transmembrane and cytoplasmic tail segments.
- The SARS-coronavirus spike glycoprotein extracellular domain consists of two hepatic areas, defined as HR1 and HR2.
- spike glycoproteins have 2 functional parts:
    1. **S1**: it is critical used for attaching to host cells with its angiotensin altered receptor enzyme 2 (ACE2) and determines host selection of viruses.
    2. **S2**: it is a subunit of the transmembrane, allowing the fusion of viral- cellular membranes.
- Fusion of membrane occurs when HRs undergo circulation modification to form a fusion center.
- Protein converts the protein's HR coiled-coil structure, known as the mucogenic state, into the hairpin-like shape of the HR area of the S protein.
- structure of this hairpin has the effect of pulling together and eventually combining the cellular and viral layers.

10. SARS-coronavirus-2 :

- SARS-coronavirus-2 is current outbreak of virus part that spread from the wuhan city, China in December 2019.

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- This coronavirus is a type of 2 virus which causes respiratory disease-2019 (COVID-19).
- It was previously known as Coronavirus (2019-nCoV), tentatively named in 2019.
- The origin of viral transmission to humans is undecided.
- But many of first people infected with the virus was workers of the Huanan Seafood-Market, and that was reported, pressure was emerging from the market.
- Few studies suggest that tourists might have brought the virus to the market, that prompted quick spread of infection.

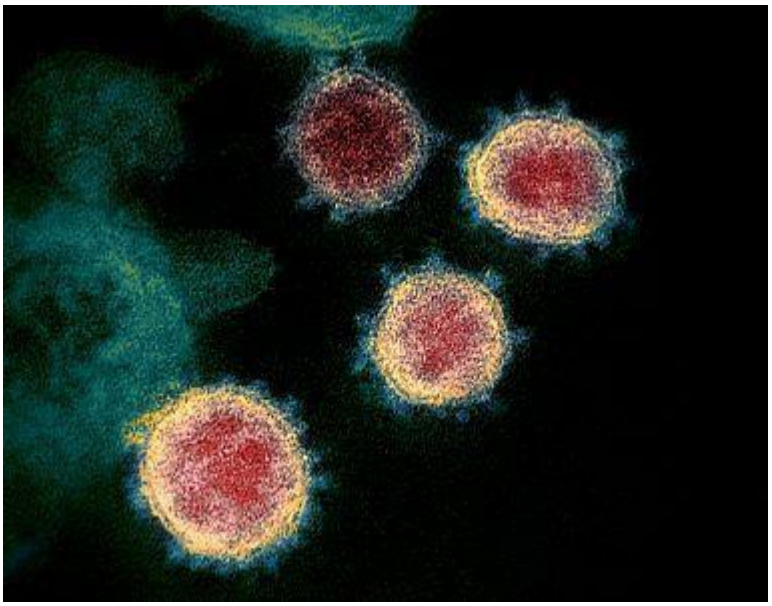

Figure.:10 electron microscope image of SARS-CoV-2

10.1 How it spread?

- Virus is reasons of COVID-19 which is spread primarily with cough, sneezing or infected droplets.
- These drops are too large to be in the air, and can fall quickly on floors or surfaces.

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- If you are close to someone who have COVID-19 infection, or touches a contaminated surface, and then your eyes, nose, or mouth, you may become diseased with the virus.
- exact transmission of virus is unknown.

10.2 prevention:

- Knowing the truth and taking appropriate steps to protect yourself and those around you.
- To prevent AR SARS-CoV-2 infection, the following precautions are taken:
    - Wash or clean hands for several times. Using hand-soap and water or alcohol hand massages.
    - Keep a distance from anyone who coughs/sneezes.
    - If you cough or sneeze then cover your elbow or mouth with your elbow or tissue.
    - If you feel sick, then stay home.
    - If you have temperature, coughing & shortness of breath, then take care of the treatment. Call beforehand.

10.3 ***symptoms:***

- Covid-19 disease has different effects on different individuals.
- Infected Most infected person has mild to moderate symptoms.
- The following symptoms are common and are similar to the SARS-CoV-1 features;
    - Fever ○

    Fatigue ○ Dry

    cough ✦

    Symptoms Other

    features consist

    of:

    - Stinging

    throat ○ Nasal

    mobbing. ○

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Runny nose ○

Aches & pains ○

Diarrhea

- On average, it takes 5-6 days for someone to show symptoms and diagnose the virus, but it can take up to 14 days.
- Symptoms in percentage; ○ 65-80% cough

○ 45% fever at presentation (85% fever during illness) ○ 20-40% dyspnea ○ 15% URI symptoms ○ 10% GI symptoms

10.4 tratment:

- There is no vaccine or drug related to this SARS-CoV-2 virus.
- Investigation treatment research is ongoing, but these treatments are in development and clinical trials to test efficacy and safety.
- Self care is taken to reduce symptoms and cure infections, including:

(according to WHO) ○ If you feel sick, you can drink a sufficient amount of fluids and eat healthy foods.

○ Live in separate rooms from further family members and use the designated toilet where needed. In addition, affected surfaces can be washed and disinfected. ○ Everyone maintains a safe life routine at home.

10.5 medical treatments:

- As you have minor indications and are well, self-isolate and contact your medical provider or a COVID-19 data line for advice.
- Take medical treatment or care, if you have a fever, a cough, and difficulty in breathing.
- Isolate & send PCR test early (may take days to result)
- GOC discussion / triage
- Notify DOH, CDC, etc
- Fluid sparing resuscitation
- Avoid NSAIDS; use acetaminophen/paracetamol for fever
- + or - empiric antibiotics

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- Intubate early under controlled conditions: RSI, no bagging, VL, have suction & capnography connected to avoid circuit breaks.
- Avoid HFNC or NIPPV (aerosolizes virus) unless individualized reasons exist (e-g. COPD, DNI status, etc); consider helmet mask interface (if available) if using NIPPV; avoid nebulizers
- Mechanical ventilation for ARDS ○ LPV per ARDSnet protocol ○ 7 P's for good care of ARDS patients: e.g.

  PEEP/Paralytics/Proning/inhaled Prostacyclins, etc ○ ?

  High PEEP ladder may be better ○ ? ECMO in select cases

  (unclear who)
- Consider using POCUS to monitor/evaluate lungs
- Investigational theraples: consider clinical trial enrolment ○ Remdesivir - not approved; used investigationally ○ Hydroxychloroquine (HCO) - available; limited evidence ○ Chloroquine (CO) - available; limited evidence ○ Tocilizumab - available; investigational for pt in shock ○ Lopinavir/ritonavir - available; recent negative RCT ○ Oseltamivir - not recommended (no evidence of efficacy) ○ Corticosteroids - not recommended (? harmful)

10.6 How SARS-CoV-2 binds to human cells:

- Viral Entry of Human Receptor Angiotensin-Altered Enzyme 2 (ACE2) to Iral Trimeric Spike Protein.
- ACE2 is a compound within the meaning of this compound.
- This structure shows how the SARS-coronavirus-2 receptor binding field interacts with ACE 2 and shows that two trimeric spike proteins can bind to the dimer of ACE 2.

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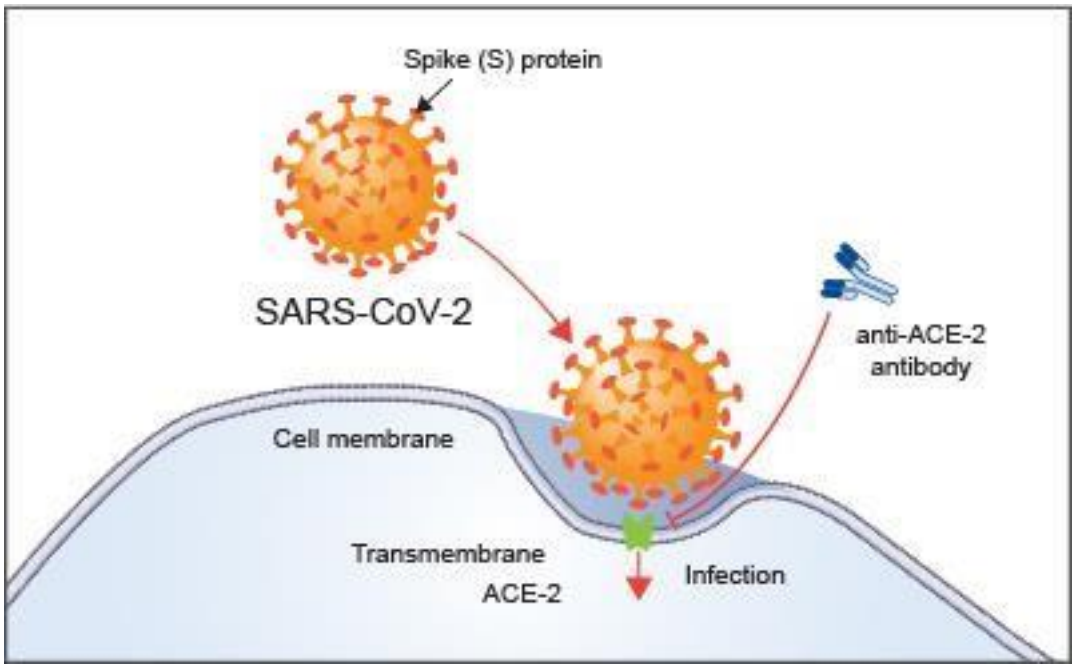

10.6.1 ACE-2 enzyme:

- ACE-2 receptor is the type 1 circulating for ACE, and has been identified as a major player in the enzyme renin- angiotensin system(RAS) and hypertensive therapy mark or a therapy target.
- It is found mainly in vascular endothelial cells, renal tubular epithelium and test cells.
- PCR studies have revealed that the ACE-2 SARS-CoV is also present in port tissues, sarcomas, kidneys, and gastrointestinal tract.
- The main substrate of ACE-2 is angiotensin II. Angiotensin 1 is reduced by ACE-2 to produce angiotensin 1–7, leading to negative regulation of RAS.
- AC It has also been shown that ACE-2 plays a protective role in the cardiovascular system and other organs.

10.6.2 ACE-2 is entry receptor for SARS-coronavirus-2 virus:

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- According to RBM order similarities between SARS-coronavirus-2 virus and SARS-corona virus, private research groups have examined whether SARScoronavirus-2 still uses ACE-2 receptor for cell penetration.
- SARS-coronavirus-2 enters ACE - 2-expressing HeLa cells using the ACE-2 enzyme from humans,Chinese horseshoe bats, civet cats and pigs.
- A monkey kidney cell line that allows replication of SARS-coronavirus with anti-SARS-coronavirus-2 anti-proteins.

10.7 Structural presentation of SARS-coronavirus-2:

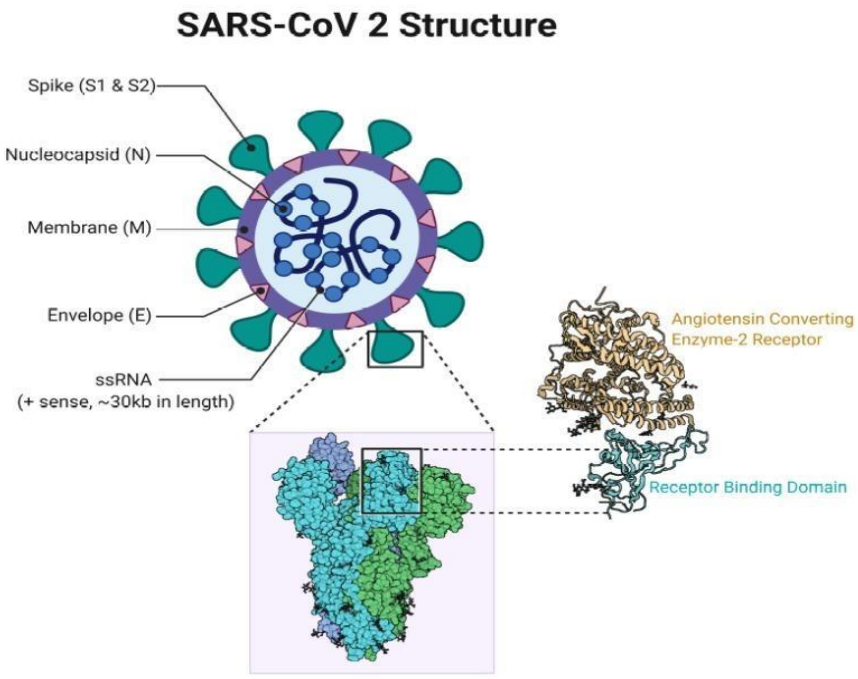

Figure.:10.7 structure of SARS-coronavirus-2

- SARS-CoV-2 virus cells are spherical like other coronaviruses.
- These coronavirus contain proteins which is called as spikes -this protein proliferate from its surface.
- spikes lock onto human cells and then results in changes of structure, which allows the viral layer, attach to the membrane of cell.
- Genes of viral arrive on the host cell to replicate and create additional viruses.

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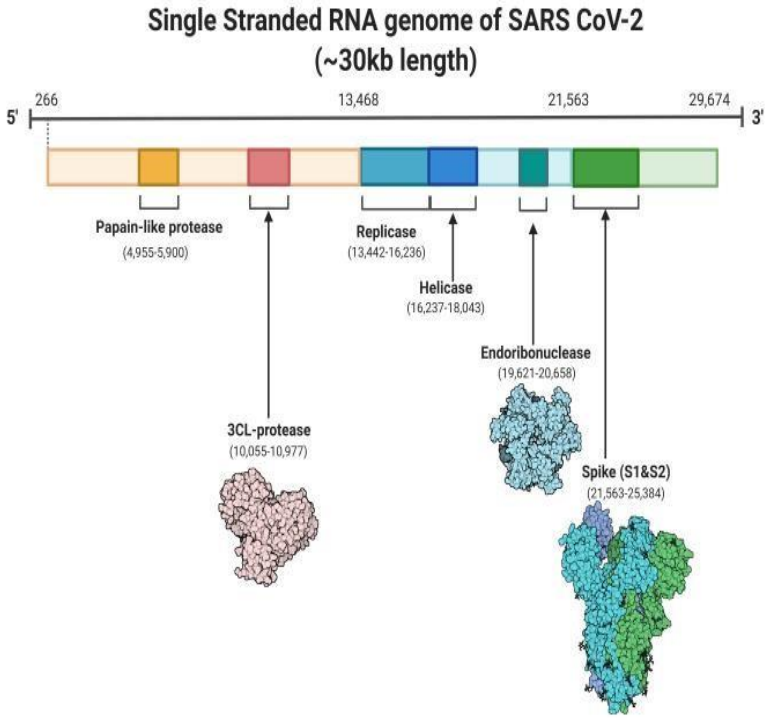
- Recent research suggests that SARS-CoV-2 spikes attach to receptors on the surface of human cells, called ACE2(angiotensin-converting enzyme 2), similar to the viruses that trigger the 2002 SARS outbreak.
- The spike glycoprotein contains 2 subunits, (S1 and S2), one of structural mechanisms of the coronavirus. homotrimers of S protein make spikes protein on the surface of virus and direct linking to host receptors.
- Note that in this current coronavirus, the S2 subunit containing the fusion of peptide, transmembrane area and cytoplasmic area is well conserved.
- So, it is targeted to antiviral components. In contrast, binding domain of spike receptor provides about 40% - the amino acid uniqueness with further SARScoronavirus.



10.8 complications:

- Chronic complications of SARS-CoV-2 infection with medically related COVID-19 disease are not yet known.
- Globally, mortality rates range between 1% and 2%.

10.9 pathophysiology:

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- Especially complex seems to have a pathogenesis that produces pneumonia.
- Clinical and preclinical research will need to clarify several aspects that underlie specific clinical presentations of the disease.
- Available data suggest that viral infections are responsible for most immune responses in the host cells.
- some cases, there is a response called 'cytokine wind'. This causes significant damage to the tissue.
- Interlukin-6 is the main protagonist of this temple. InterLukin-6 is derived from stimulated leukocytes and turns on a large number of tissues and cells.
- Coronavirus stimulates the distinction of B lymphocytes, encourages the development of some cell groups and hinders the growth of others.
- They also promote the development of acute phase proteins and acts as a key role in thermoregulation, bone maintenance and central nervous system function.
- While the main function of IL-6 is pro-inflammatory, it also has antiinflammatory effects.
- Through inflammatory diseases, allergies, autoimmune disorders, cardiovascular diseases and certain types of cancer, IL-6 is increased.
- It is involved in cytokine release syndrome (CRS) pathogenesis, a severe systemic inflammatory disease such as fever and multi-organ dysfunction.

11. DIAGNOSTIC TEST:

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✦ Diagnostic tests are used to demonstrate the positive or negative of the infection. These tests also find evidence of past infection.

- Highly sensitive and specific molecular tests ○ The results will be ready in 10-15 minutes.
- Serological examination used to determine the present and past functioning of the infection

1. For molecular test:

- The virus is detected a few days after the onset of symptoms.

2. For serological test:

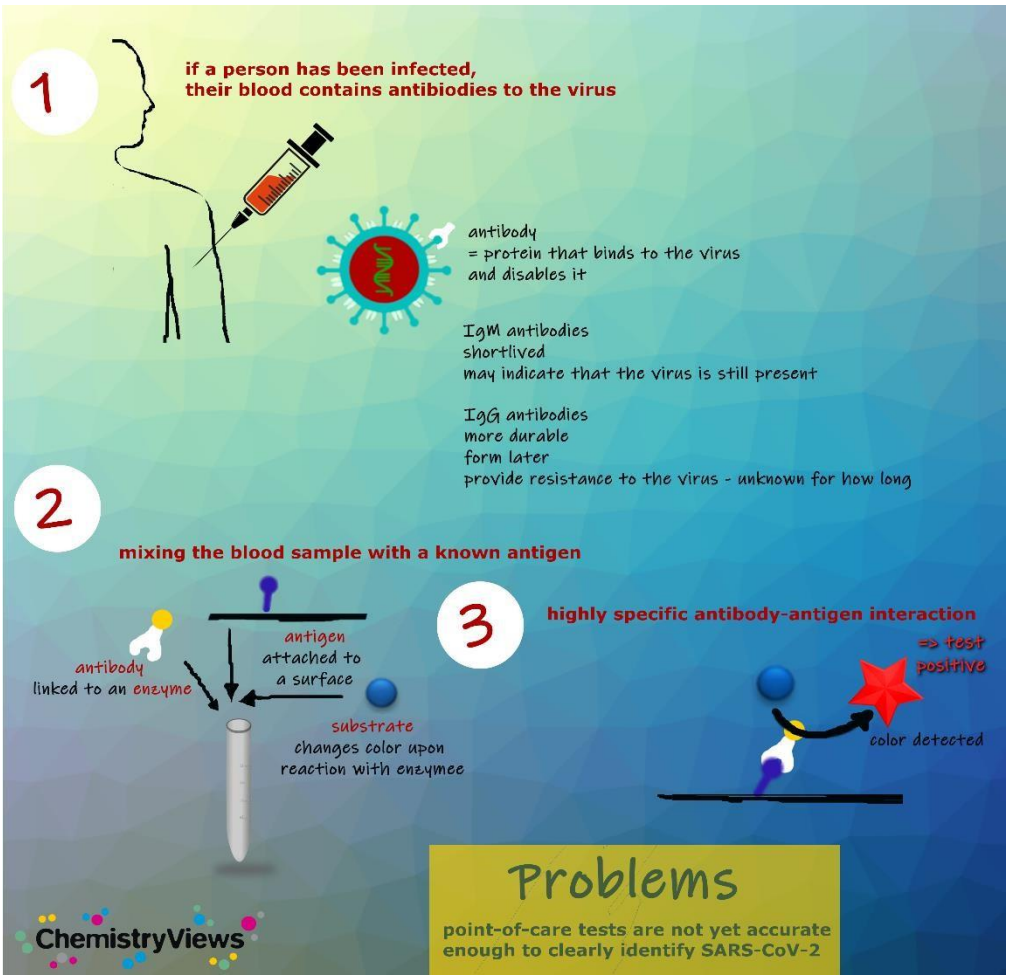

Figure.:11 serological testing steps

- 5 days after onset of symptoms, patients develop an antibody response.
- The first antibody response is IgM antibody. It may persist for a few months. High level of IgM suggests that the infection is active.

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- As IgM antibody subside, IgG antibody levels starts to increase. And it may persist for a long time.
- In this test, sample of patient are taken at the acute & convalescent stage of infection.
- If there is a appearance of 4-fold rise in IgG antibody, it is the evidence of infection.

11.1 For COVID-19:

- ✦ There are more than 20 different molecular tests for V Covid-19.
- ✦ These tests are available to identify the genetic material of the test virus (RNA).

A. **Upper respiratory specimen:** ○ Nasopharyngeal and oropharyngeal swabs are taken as test specimens. B. **Lower respiratory pattern:** ○ sputum; (If possible, for patents with productive cough.

- Broncoalover

Loves (BAL) C. **For**

Patents:

- Those who are

hospitalized ○ Take

blood samples.

- ✦ All samples collected at clinics.
- ✦ These samples of samples are given to a central laboratory with factors and equipment to test for indication of COVID-19 disease.
- ✦ The positive outcome of the test illustrates the presence of the virus in the specimen samples, i.e. the infection is confirmed.
- ✦ The negative result of the test explains the absence of the virus in the tested samples, which means there is no infection.
- ✦ If the patient has a negative result and symptoms show, the test is repeated and patients should remain in quarantine mode.
- ✦ The detection of other coronaviruses or novel coronaviruses does not confirm the initial positive outcome of infection.

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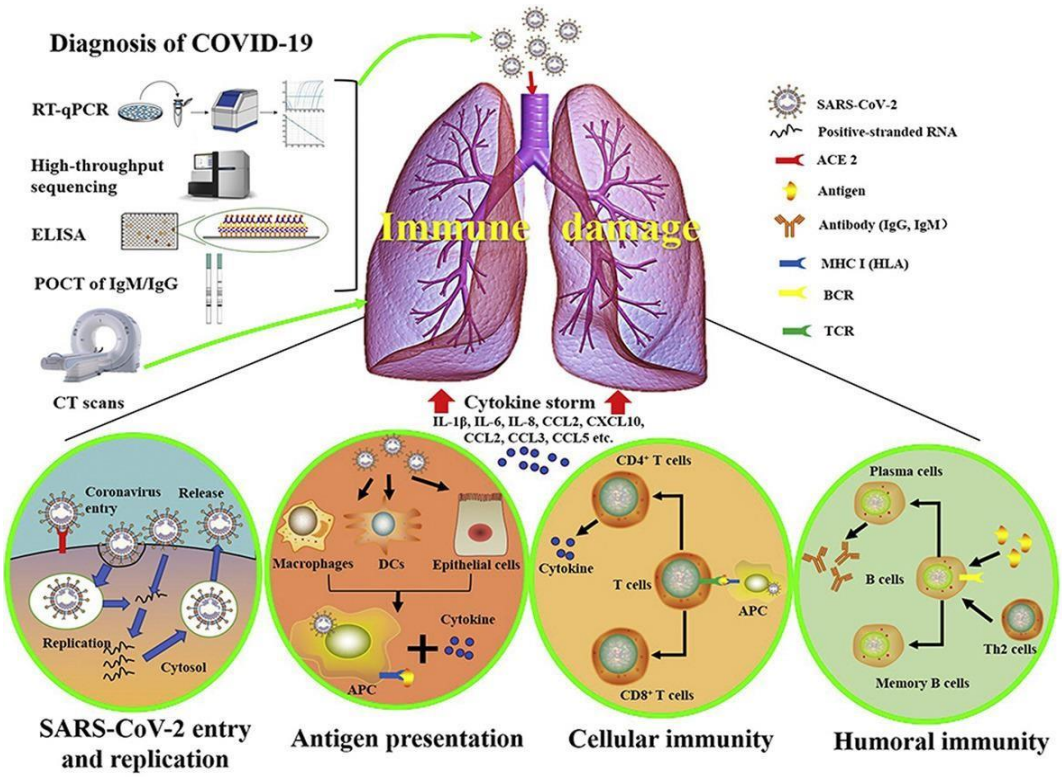

Specimen type	Collection materials	Storage temperature until testing in-country laboratory	Recommended temperature for shipment according to expected shipment time
Nasopharyngeal and oropharyngeal swab	Dacron or polyester flocked swabs*	2-8 °C	2-8 °C if ≤5 days –70 °C (dry ice) if >5 days
Bronchoalveolar lavage	Sterile container *	2-8 °C	2-8 °C if ≤2 days –70 °C (dry ice) if >2 days
(Endo)tracheal aspirate, nasopharyngeal or nasal wash/aspirate	Sterile container *	2-8 °C	2-8 °C if ≤2 days –70 °C (dry ice) if >2 days
Sputum	Sterile container	2-8 °C	2-8 °C if ≤2 days –70 °C (dry ice) if >2 days
Tissue from biopsy or autopsy including from lung.	Sterile container with saline or VTM.	2-8 °C	2-8 °C if ≤24 hours –70 °C (dry ice) if >24 hours
Serum	Serum separator tubes (adults: collect 3-5 ml whole blood).	2-8 °C	2-8 °C if ≤5 days –70 °C (dry ice) if >5 days
Whole blood	Collection tube	2-8 °C	2-8 °C if ≤5 days –70 °C (dry ice) if >5 days
Stool	Stool container	2-8 °C	2-8 °C if ≤5 days –70 °C (dry ice) if >5 days
Urine	Urine collection container	2-8 °C	2-8 °C if ≤5 days –70 °C (dry ice) if >5 days

12. PCR testing used for SARS-Coronavirus-2:

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✦ Clinical trials for novel SARS-coronavirus-2 coronaviruses are performed using **three** methods:

a. whole genome sequencing
b. real-time reverse transcriptase PCR (rRT-PCR)
c. serology.

- ✦ Novel Sequencing has been used for the primary detection of this novel virus, especially at the beginning of the outbreak, and is mainly a viral discovery method.
- ✦ Each clinical trial for AR practically SARS-CoV-2 is currently underway using RRT-PCR.
- ✦ Serological tests that identify previous infections are now being developed and explored in a separate fact sheet.
- ✦ Viral cultures can also be used in exceptional cases, but they are not common practices in medical practice and are not discussed here.
- ✦ The CDC recommends that physicians use their best judgment to determine if the patient meets the patient's test criteria, and the common symptoms are coughing, acute respiratory disease, and shortness of breath.
- ✦ Tests Preferences:

1. **Entering Patients and Health Workers**: Providing adequate treatment to patients already admitted, preventing infections by health care providers, and reducing the risk of health-related infections.
2. **Patients at risk**: Patients in long-term care facilities, patients over the age of 65, comorbidities (diabetes, heart disease, chronic lung disease) and symptomatic first responders.
3. **Community screening:** Population (COVID-19 hotspots) with significant (required) staff, asymptomatic healthcare workers, first responders with symptoms, and high rates of COVID-19 hospitalization.

12.1 PCR testing steps:

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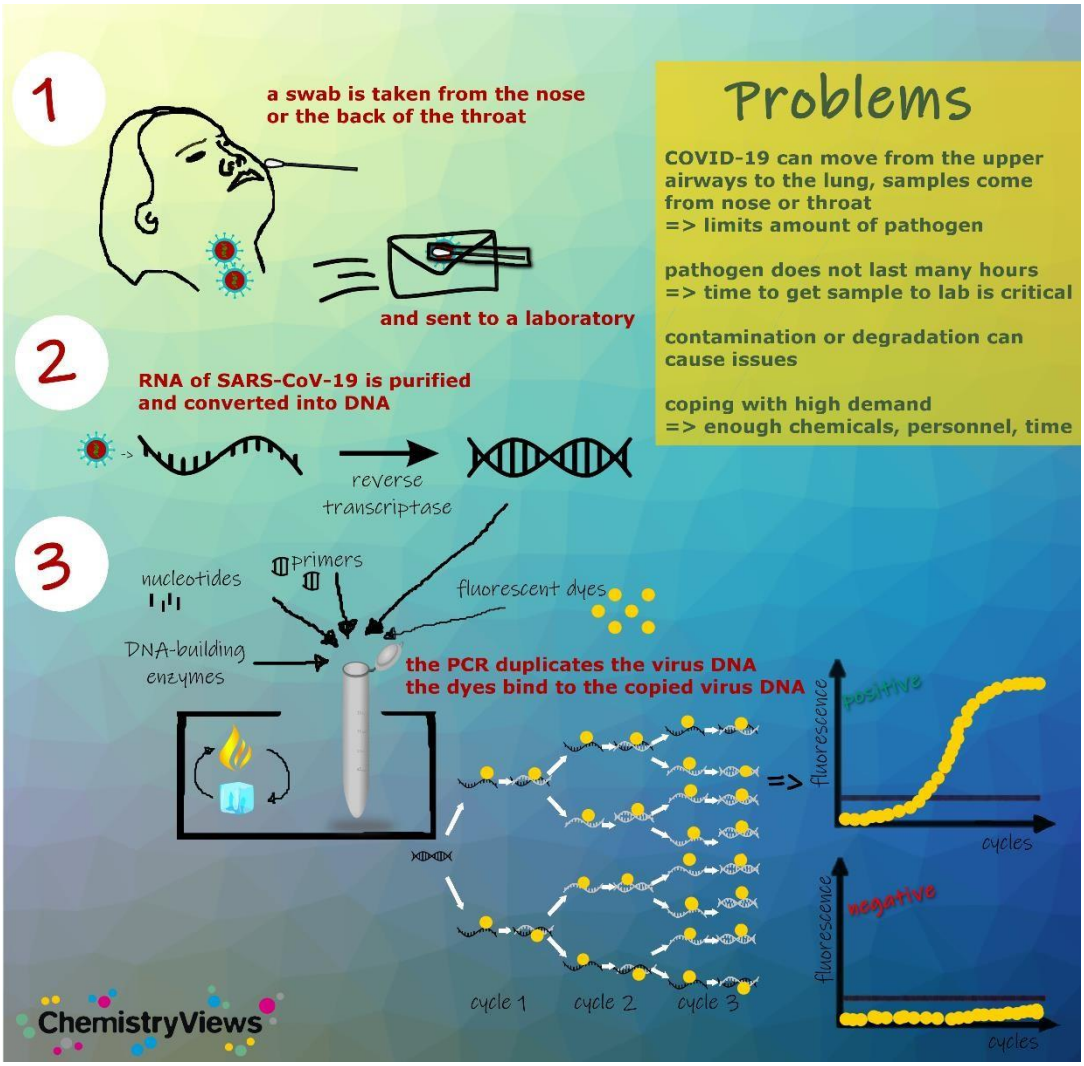

Figure.:12.1 PCR testing steps

- The R PCR test notices the genetic data of the virus, RNA. This is possible when virus is present and a person is actively infected.
- PCR tests are used to directly determine the body's immune response or the presence of antigens instead of antibodies.
- By identifying the viral RNA that must be present in the body before the development of antibodies or the onset of infectious symptoms, tests indicate that anyone has the virus very quickly.
- PCR gives us a clear idea of who is infected. You must separate and get in touch with the people you contact, so that they too can be detained.
- This is the real benefit of the latest large clinical trials, you can discontinue that transmission cycle and get a better picture of what is happening. Senior Lecturer in Microbiology, University of Sussex.

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- By scaling up PCR tests to screen large numbers of nasopharyngeal swab specimens in a community, public health officials can get a better picture of the spread of the disease population, such as Covid-19.
- PCR tests are very labor intensive, and errors between models and analyzes can be multiple stages.
- PCR false negatives can last up to 30% of the time with different PCR tests, which means they are more useful for diagnosing the presence of infection than explicitly giving it to the patient.
- Honorary Clinical Lecturer Dr. Warwick Medical School James Gill said: During the outbreak, PCR testing was enhanced by early screening techniques and more automation was introduced to eliminate errors. As such, we now have the usual 80-85% -i.e. The test is likely to detect the virus.

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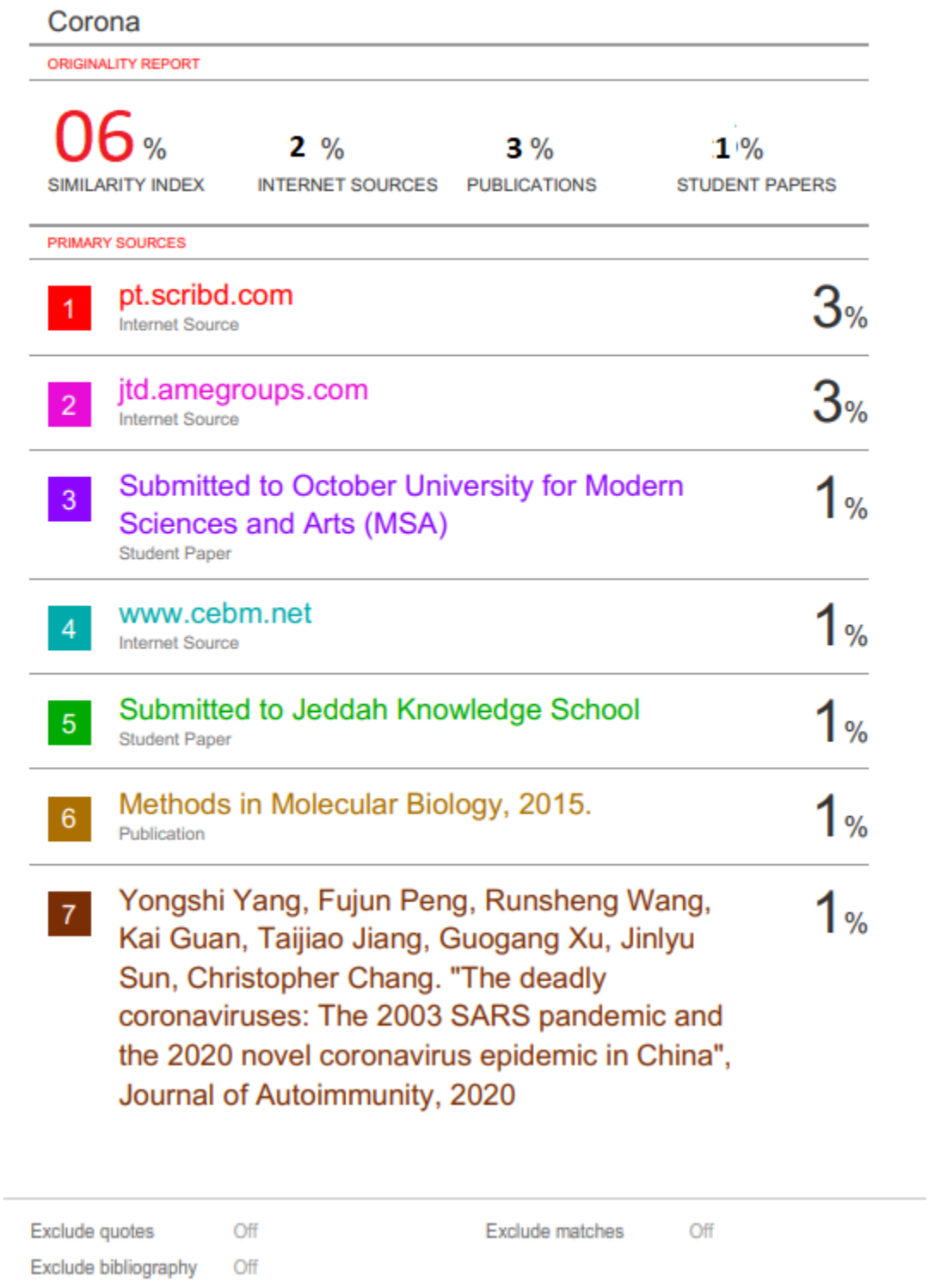

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