

Review Article	Pak-Euro Journal of Medical and Life Sciences
DOI: 10.31580/pjmls.v5i3.2606	Copyright © All rights are reserved by Corresponding Author
Vol. 5 No. 3, 2022: pp. 541-554	
www.readersinsight.net/pjmls	
Submission: June 09, 2022	Revised: September 11, 2022 Accepted: September 26, 2022

A REVIEW OF COVID 19 PANDEMIC

Zohaib Raja¹, Attaullah Jaffar^{1*}

¹Department of Microbiology, University of Balochistan, Quetta, Pakistan

*Corresponding Author: Attaullah Jaffar. E.mail : atta.uob@gmail.com



Abstract

The outburst of the corona virus is new to the world however this disastrous virus had been between us since 1960s till 2019 when it was considered to only cause respiratory disease however since its pandemic the scientists focused more on this virus and new research is being conducted to know more about it. In this review article we focused on knowledge or research that is already present including the background of the virus and its pathogenicity along with its history, epidemiology, way of infection, clinical symptoms of the disease how to diagnose it and use of medicines to overcome the disease as well as preventive measures to avoid being infected with the virus.

Keywords: Diagnosis, Epidemiology, MERS, Pathogen's structure, Prevention, SARS-COV-2

INTRODUCTION

Many times, history changed itself due to rising periodic pandemics devastating humankind. These outbreaks are not new to the world and mankind and at present mankind is fronting a serious pandemic called Coronavirus disease 2019 or simply COVID19 that has encountered millions of people in the world (1).

It's not a single time a pathogen threatened humankind but in different eras different pathogens have frightened humankind and forced world challenges to humankind and its health. Most of the time these pathogens were successfully suppressed and were not allowed to cause huge distress and deaths. However, there are some outliers that breakout of this rule due a unique way of pathogenicity in nature or due to humankind failing to suppress the pathogen in a specific area. This Novel coronavirus is one of them that is also known as SARS-COV-2 (severe acute respiratory syndrome coronavirus 2) as it constantly extends throughout the world as a disastrous pandemic due to its differentiated and deceptive appraisal of its correct contact (2).

It was almost close to the year of 2019 when this disastrous disease of COVID19 came to the world's knowledge of world. The infectious pathogen that leads to this disease was recognized using next generation sequencing techniques as Novel coronavirus or ncoronavirus and it was found to be similarly associated with SARS-coronavirus that caused an epidemic in 2003. On the authority of world health organisation (WHO) instruction this ncoronavirus was termed as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Initially the reports arise from the Wuhan city of China present in Hubei province and first report was reported in December of 2019. This disease of covid 19 quickly started to outspread throughout the world and months later of first identified case in March 2020 WHO announced the disease as pandemic (3). In humans and vertebrates, the coronaviruses have an importance as pathogens. These coronaviruses can infect the respiratory system along with gastrointestinal tract as well as central nervous system of human beings' animals' birds' bats etc. This pathogen is not new and caused an epidemic in 2012 and that time its strain led to SARS 2012 and had enough proof of being transmitted to human to human and animal to human and that helped to recognize transmission of this ncoronavirus (4).

This coronavirus family is a big family of pleomorphic individuals having a crown shape being covered with envelop and are single stranded positive sense RNA viruses. They are grouped in the order Nidovirales in family coronaviridae and sub family coronaviridae. So far there have been hundreds of coronaviruses discovered and a large portion of their family infects mostly animals and are zoonotic in



nature and can infect humans through animals and other animals too such as bats, pigs' cats and camels. Corona viruses are divided into four major genera of RNA viruses that are infectious to mammals named alpha beta gamma and delta coronaviruses. Till this of these four genera's only initial two genera's alpha and beta have been recognized in human beings and the other two gamma and delta are found in only animals specially bats that present themselves as biggest host (5).

This group of corona viruses is not a small group and is a big group that also contains varied types of strains leading from common cold to disastrous disease like SARS (severe acute respiratory syndrome), MERS (middle east respiratory syndrome) and COVID19. This coronavirus commonly transfers between mammals and birds. But so far human to human transmissible coronaviruses have also been identified that are seven in number. Coronaviruses are naturally zoonotic means they transmit through animals to other animals and humans. Of the seven-corona viruses four of them named 229E, HKU1, NL63 commonly cause common cold in human beings without causing serious infection. But in recent decades some of coronaviruses such as SARS COV 2003, MERS COV 2012 and SARS COV-2 has overall changed every knew aspect of the coronaviruses as from causing simple cold to leading to deadly infections infecting mostly respiratory tract such as just before 2020 the ncoronavirus emerged from China Wuhan and become deadly. It was 31st January 2020 when WHO announced it as epidemic and forced emergency because of its nature and in march 2020 declared this COVID 19 disease as pandemic as it started to outspread throughout the world leading to infect millions of people and causing thousands deaths (6).

Fig. 1 is a presentation of the lineage of coronavirus family coronavirinae that presents various subdivisions of the family. Based on taxonomy, the family of coronaviridae is divided into two subfamilies, toronovirinae and orthocoronavirinae. Sub-family orthocoronavirinae is sub categorized into four genera named alpha beta gamma and delta coronaviruses being grouped in order nidovirales. According to various researchers it has been identified that even coronaviruses are present in various species of animals but two of them alpha coronaviruses and beta coronaviruses also cause infections in humans (7).

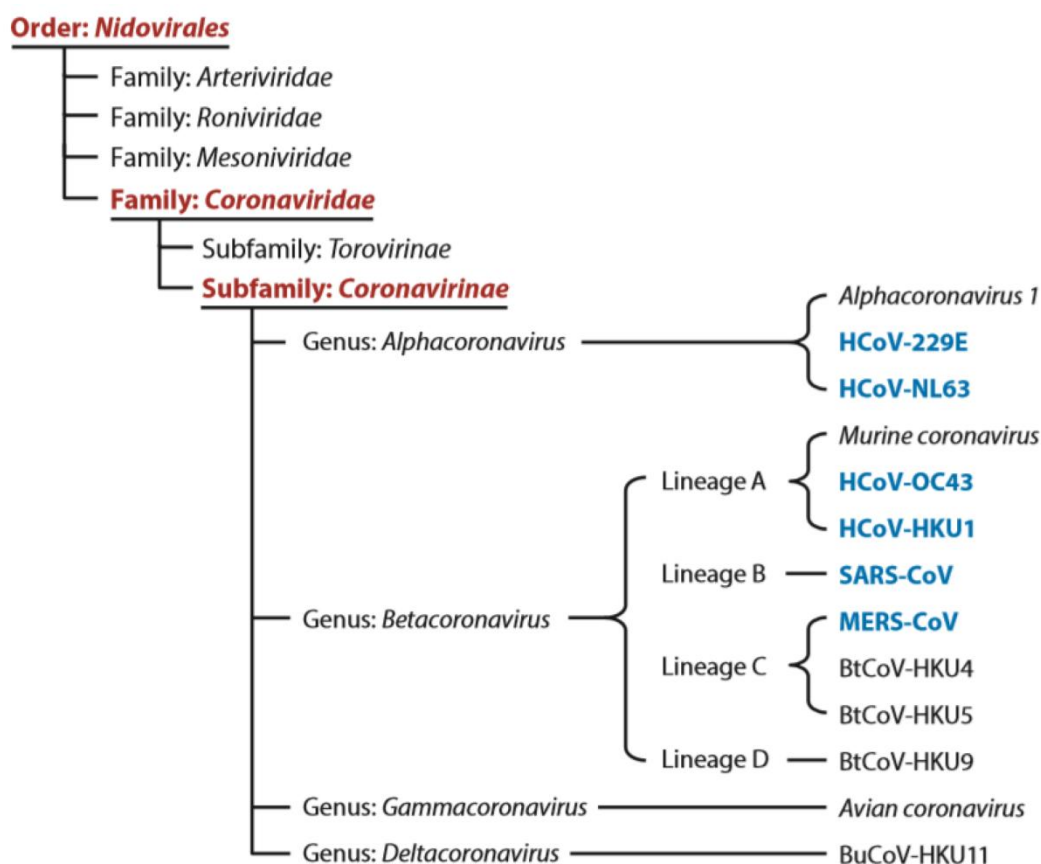


Fig. 1. Classification scheme of HCoV and other coronaviruses (Altaf R et al., 2021)

As said, corona viruses have an envelope and are single stranded positive sense having RNA genome and their size ranges between 60 to 140 nm in diameter having spikes on the surface that makes it appear crown shaped when looked under electron microscope (8). Major transmission occurred through human to human by respiratory droplets. However, there are other ways for viruses to spread such as

contact with contaminated surfaces or enteric as the virus has ability to survive for some time on surfaces and may be present in faeces. Persons without having symptoms and being carriers can also transmit the disease. After entry to the body through droplet contact or other means it attaches to the receptors ACE2 present on type 2 pneumocytes in the respiratory tract. The incubation period for the virus is between 3 to 12 days but there may be some differences in some patients. Also there are proofs about mutation in virus genome and also in different regions different strains have been identified and being infectious to people (9). It should be noticed and highlighted that droplet contact is not only the major transmission way as it may also spread through biomedical waste produced by hospitals or stations having COVID 19 patients. There should be highly strict rules to avoid this type of outspread and for that new ways to disinfect the biomedical waste are being discovered (10). No doubt about the origin of the disease or pathogen from animals but the considerable way of disease being transmitted is from person to person like SARS coV 2003 and MERS coV 2012. Major way of COVID 19 disease to spread is by droplet contact after someone being infected sneezes or coughs and releases the pathogen in air that settles down on surfaces but there are enough chances of disease to spread also by airborne by breathing in contaminated air or environment, by faecal contamination and maternal foetal transmission. It should be marked that a person infected with COVID 19 can fully transmit the pathogen before arising of symptoms (11).

Corona viruses have a RNA genome that consists of genes for four structural proteins that make envelope of virus (E), membrane of virus (M), nucleocapsid of virus (N) and viral spikes (S). These structural genes make the virus lipid bilayer enveloped entities giving them differences in size distinguished by spike-like projections on its surface just like flower petals. In the centre of the virion particle there is a nucleocapsid having icosahedral conformity that holds its electron dense layer whose centre is lucid. As the virus has positive sense single stranded RNA so it uses a negative RNA replication strategy that produces the RNA that can be directly used to translate the genome into viral components that lead to formation of virions. There are also accessory proteins present in the core that vary from each other (12).

It takes time to show symptoms after a person gets infected with a virus and the time varies from person to person between 6 to 41 days with 14 days of medium, this variation of time is because of the difference in immunity of persons. Patients with an age of greater than 70 allow the virus to have shorter incubation of virus than the patient's underage of 70. Moreover, people with prior chronic disease such as diabetes, hypertension, asthma etc are more at risk of being infected. Initial symptom of respiratory is shortness of breathing that appears within 5 days after being infected or after the first symptom. As shortness in breathing appears days after infection therefore patients are also being admitted to hospital after 5 to 7 days and after that person infected show other symptoms from nonspecific clinical presentations to respiratory clinical presentations including spitting of blood because of damaged lungs, pain in chest and other respiratory illnesses (7). Patients may be non-symptomatic to having symptoms like flu, temperature, and complex breathing difficulty to serious clinical manifestations such as injury to lung or other organs (1).

Still knowledge about history of patients, major clinical presentations and other diagnostic methods are required to identify the disease. At present the most reliable method to detect the disease or pathogen is real time PCR of samples taken from mouth or nose (13). Molecular tests can also be done to diagnose sputum or other secretions of the respiratory tract. Also virus has been identified or present in faeces or blood in serious conditions (8). Also ELISA and rapid diagnostic tests are among serological diagnosis tests that help to identify the pathogen and its antibodies produced against the specific pathogen causing COVID 19 disease (14).

So far not a single antiviral therapy is present to cure the COVID 19 disease caused by SARS-COV-2. Therefore, focus is to enhance the immune system of patients to suppress the symptoms and patients with severe infection or illness are given supportive therapy such as artificial oxygen therapy and hemodynamic therapy. Along with that scientists are researching to find ways to stop or even decrease the transmission or virus and studying different drugs to treat the disease. So far there is not enough evidence of any single antiviral drug that helps to cure the COVID 19 disease and therefore the US Food and Drug Administration (FDA) has not approved any of drugs to be given to patients infected with SARS-COV-2. Many drugs such as chloroquine, remdesivir, arbidol, and favipiravir are still under research to test their effect and safety for

therapy of COVID19 disease. Some of these drugs are under trials and may soon be available to treat the disease (9).

As no treatment and cure are available to overcome the disease, the foremost way to overcome the disease is to stop the spread of infection on time and keep away of being exposed to the pathogen. Because of this, countries throughout the world are now concentrating standard operating measures (SOPs) such as isolation, social distancing, quarantine and banning public gatherings to avoid the spread of virus. Individually exposing of virus can be avoided by using facemasks, washing hands with soaps regularly, good air ventilation in rooms, personal hygiene and keeping away from crowded places (4).

HISTORY

Corona viruses are not to mankind and had previously caused severe infection to people in different countries. First time this pathogen was identified in 1965 when the pathogen caused respiratory illness and was discovered from respiratory secretions of patients infected with common cold and at that time was named B814 by Tyrrell and Bynoe. Before this pandemic of COVID 19 some strains of corona viruses named OC43 and 229E led to epidemics in different areas of the world in three decades and their main targets were children. Additionally with time three more species of corona viruses being able to infect humans were discovered and were named human coronavirus NL63 (Hcov-NL63), human coronavirus-hku1 (Hcov-HKU1) and MERS- Cov in different eras. Of these viruses HCoV-NL63 infected infants causing bronchiolitis in infants in 2004 while Hcov-HKU1 was found in patients infected with pneumonia in 2005 in Hong Kong. It was 2002-2003 when in south China a new disease was discovered named SARS-Cov arises and was the first pandemic of 21st century and outspread in the world causing many deaths. After studies it was found that this SARS-cov has connections with using wild animals for human consumption in the meat market of Wuhan city of China in Hubei province having a population of 1.4 crore. This new virus is transmitted between humans around the world due to the travelling of infected persons by air and lead to infection of 8089 persons leading to deaths of more than 700 people in the world. This epidemic was the 6th public health emergency by WHO (1).

It was a normal end of 2019 like other years before in December a disease emerged in Wuhan city of China named initially Wuhan pneumonia. The virus was identified as a novel coronavirus that belonged to the genus of corona virus beta coronavirus and sub genus of sarbecoronavirus. The disease was later named as 2019 n-cov or SARS-COV-2 that quickly spread in the world and was regarded as the third zoonotic disease of 21st century that infected humans (1). Before this third infection caused by zoonosis there were previously two diseases where beta coronaviruses of animals came in contact with humans and led to serious infections. The first time it was happened in 2002 because of a new beta coronavirus that uses bats as a reservoir to infect humans through cats in the province of China Guangdong. This newly emerged beta corona virus was named as severe acute respiratory syndrome coronavirus and it infected more than 8 thousand people largely in China and honking and lead to murder of more than 900 people with a death rate of 11% before being suppressed. After a decade to the first zoonosis in year of 2012 the new coronavirus emerged in Saudi Arabia and was named Middle East Respiratory Syndrome Coronavirus (MERS-Cov) that too belonged to bats as host and spread through camels infecting more than 2 thousand of people with killing more than 8 hundreds (8). As studied coronavirus were discovered in 1960 decade and since then has been infecting humans such as in a study in 2001 in Canada more than 500 persons had flu like symptoms and upon diagnosis by polymerase chain reaction it came to known that 3.6% of these infected persons were positive for being infected with Hcov-NL63 strain of coronavirus. Before the first disastrous outspread of coronavirus in 2002 from Guangdong province of China that caused many deaths throughout the world with countries such as Thailand, Taiwan, Vietnam, and even united states of America causing severe acute respiratory syndrome with, this virus was not considered as deadly was treated as common virus. Following this outburst of 2002 the scientists and specially microbiologists started to study this unique infectious virus and its way of causing infection to overcome it. As this deadly virus in 2002 to 2004 caused more than 8 thousands of deaths therefore in 2005 WHO declared an emergency state on it (15). This virus of COVID 19 disease named SARS-cov-2 has been classified to different categories in which it falls in the order

of nidovirales, family of coronaviridae, and sub family of orthocoronavirinae. The sub family is further divided into 4 groups named alpha, beta, gamma and delta coronaviruses of which alpha and beta coronaviruses infect humans and gamma and delta coronaviruses mostly take animals as their hosts. This novel coronavirus spreads from animals to humans as it is a zoonotic virus but once after it infects humans it also transmits between humans mainly through air droplets. Of the animals that transmit through them the biggest reservoir as host for this virus are bats. But it may also reside in other animals such as cattle, turkeys, pigs, mice, camels, cats and dogs (12).

As so far studied COVID 19 disease is caused by novel coronavirus belonging to beta coronaviruses now termed as severe acute respiratory syndrome coronavirus. Its first case was detected in Hubei province of China in city of Wuhan on 31st December of 2019 as the disease started spreading quickly and started high death tolls so on 30 January 2020 WHO declared an emergency and couple of months later in March 11 2020 WHO declared this disease as a pandemic (5). This study has been done to gain better general knowledge about the COVID19 disease, its pathogen, its history epidemiology, pathophysiology transmission symptoms diagnosis treatment and prevention using previous work on this disease.

PATHOGEN AND ITS STRUCTURE

Infectious agent that leads to the disease COVID19 has been identified at the end of January 2020 and has been termed SARS-cov-2 and is a virus (13). This virus has been classified into order Nidovirales, to family coronaviridae and sub family of coronaviridae. The sub family is further divided into 4 genera named alpha beta gamma and delta coronaviruses. The virus has an RNA genome that is also a single stranded positive sense genome that can use its genome directly as mRNA with size of 30kb and with 5'-cap structure and 3'-poly-A tail. The virus uses its genome as mRNA that encodes structural and non-structural proteins of the virus and to form replication transcription complex in double membrane vesicles(4). Study of virus using an electron microscope has given information about SARS-cov-2 virus about its 3d structure and it came to up that the virus is pleomorphic in nature means is round or oval and its nucleocapsid is helical in structure and have projections on its surface that give it crown like presence. Also the virus has an envelope made up of three structural proteins named S, M and E that covers the genome of the virus(16). The appearance of corona viruses is spherical in shape and has an average diameter between 80-120nm and consists of many projections appearing out of its surface of envelope of virus. The four major structural proteins that virus consists of are glycoprotein spikes (S), the envelope protein (E), nucleocapsid (N) and matrix protein (M). The open reading frame region (ORF) of viral genome that encodes for structural proteins also encodes for non-structural proteins including papain like protease, 3-chymotrypsin-like protease as well as RNA dependent RNA polymerase. The projection present on the envelope or surface of the virus helps it to attach to the receptors of the host cell that depend upon the receptor binding domain (RBD). Based on attachment of virus to host cell receptors, the S protein of the viral structure is broken into subparts named N-terminal S1 and C-terminal S2 subparts by protease enzymes of the host cell (14).

As studied these viruses are spherical in shape but still are pleomorphic means can alter their shape with a varying size in diameters that ranges between 60-220nm and have projections on its surface that have a length of about 20nm. there is a presence of clear electron dense shells pair. In study of negatively prepared stains the inner components are not clearly visible (17).

The three structural proteins of the virus encoded by its genome have different and specific functions. Studies show that the N protein of virus structural proteins is involved in the replication of the genome of the virus. The other structural protein named M protein plays a key role in the maturation of the virions and it's his job to identify where new virions will be assembled. The last structural protein named S has a key role as it plays the most important role in attachment of the virus to the host cell receptors without which further infection can't be processed (18).

GENOME

The studies have shown that among the RNA viruses coronaviruses are the group of RNA viruses that has the biggest genome in size that ranges between 27 to 30kb in size. The genome of corona viruses is

not simple and are complex as their genomic material is arranged into 6 or 7 different domains and each domain consists of either one or more than one open reading frames (ORF) that codes for proteins and these ORFs are split by junction sequences which consist of signals that work for transcription of the genome to the proteins (18). This genome of corona viruses ranges between 27 to 3kb in size and is a long with no fragments and is single stranded RNA being positive sense and codes for more than 9 thousand amino acids. The untranslated regions of genome that make 5' end and 3' end of the genome consist of 265 and 358 number nucleotides respectively. These nucleotides present at 5' end and 3' end of the genome of SARS-cov-2 are more than 83% similar to other beta coronaviruses (14). There are genes for structural proteins for corona viruses that encode envelop (E) of coronaviruses, membrane of coronaviruses (M), nucleocapsid of coronaviruses (N) and projections present on surface of corona viruses named spikes (S). Along with that corona virus's genome consist of genes that make coronaviruses lipid bilayer enveloped viruses with variation in sizes of new virions distinguished by many spike-like projections of 20nm in length that appear on its surface and gave it crown like projection. At the centre of virus, the genome is held in nucleocapsid that is icosahedral in structure and has electron dense layer. The genome of corona viruses requires negative RNA replication cycle to produce sub genomic protein encoding RNAs along with genomic RNA for newly formed virions assemblage. In the core of the viruses there are also accessory proteins that have different functions and structure when compared to different strains of corona viruses (12).

EVOLUTION OF CORONAVIRUS

So far, the studies had concluded that the lowest fatality of SARS-cov-2 is between 2% to 4% and the highest fatality rate that is serious that that is as 10% in more inhabited cities such New York of United States of America. There have been far more fatalities that have been reported in low time span when this disease is compared to SARS-Cov-1 and MERS-Cov. This disastrous variation upon deaths when compared to SARS-cov-1 and MERS even with more than 80% resemblance to SARS-Cov-1 and more than 50% resemblance to MERS-Cov is attributed to the censorious mutations that occurred in the genome of SARS-Cov-2. Because of these mutations the ability of SARS-Cov-2 to infect the targeted host cells and enhanced its ability to speed up its way of pathogenesis. The studies so far been done has detected up to between 6 to 9 mutations in the total genome of SARS-Cov-2 in the open reading frames of viral genome that have been outlined from varying countries of the world (16).

EPIDEMIOLOGY

Currently the world is facing a serious threat from pneumonia like disease that is extremely contagious so far has taken up most of the areas of the world that are inhabited by humans and is termed as coronavirus disease 2019 or simply COVID19 disease. Because of the quick spread of this covid 19 the WHO declared an emergency on 30 January 2020 and a couple of months later declared it pandemic. It did not take more time to spread from its origination state from Wuhan city of China and spread more quickly to the entire world. The number of countries being infected with this covid 19 quickly started to increase in no time according to WHO daily report. WHO is reporting daily base number of infections but it is estimated that the number may be much greater than what has been reporting because it is not easy to identify each and every case and also there are people infected that does not show any type of symptoms and there are poor countries that do not have enough of strength in means of money and other means to be able to detect and identify all of the cases. Moreover the SARS-cov-2 because of its mutation has the ability to infect more people than its predecessors like SARS-cov-1 and MERS-Cov, which was infected in 2002 and 2012 respectively and lead to thousands of deaths collectively in just 27 countries (5).

People of all ages are liable to Covid 19 disease while elderly people are more at risk of infection (19). The major cause of this disease to spread so quickly is the generation of air droplets by infected persons but it has been proved that people infected with virus without any symptoms may also transmit the disease to the healthy persons. Also, the studies have shown that there is an increased presence of virus in numbers in the nasal cavity than throat while both patients with symptoms and no symptoms have similar load of virus (20). A patient can be infected even after symptoms are gone or even being recovered medically. There is a chance that some of infected person may act as remarkable spreaders and a case like that have been

reported where a citizen of United Kingdom came to attend a conference in Singapore and before getting back to United Kingdom, he had infected at least 11 persons that have been reported and there may be more that has not reported (8). When an infected person sneezes or coughs he releases a load of virus into the air in the form of air droplets that may travel up to 1 to 2 meters and may settle down on surfaces or objects we use(21). The concerning thing about it is that the virus can survive on these surfaces and objects for several days, but the good thing is that they can be killed within a minute when exposed to common disinfectants such as sodium hypochlorite, hydrogen peroxide etc. Virus enters the body either by breathing in contaminated air or after touching contaminated surfaces and touching mouth or nose or eyes without washing hands. Stools are also a source of transmission as the virus resides in the stool of infected persons and contamination of drinking water with infected stool contamination leads to the infection with the virus (21).

There must be a discussion about the concept of RO when studying the spread of COVID19 from one person to another. RO can be defined as the reproductive ratio or more simply the degree of transmissibility of pathogens from one person to another. After studying RO, it can be detected that how many persons can get disease from one single infected individual. Studies regarding COVID19 have shown that R for COVID 19 disease is between 2 to 4 persons. So, it means that one single person infected with COVID 19 has the capacity to infect 2 to 4 persons (22). The best way to decrease chances of transmission of COVID19 disease is to have specific distancing from other individuals and separating infected persons from healthy ones and by doing this risk of contracting with infected air droplets can be avoided (7).

The fastest way of COVID 19 disease transmission is by air droplets produced by infected persons. It's not clear yet that the pathogen enters the body through eyes, but the SARS-Cov-2 pathogen has been detected in tears. As we talked about RO of COVID 19 that ranges between 2 to 4 but it's still not accurate as gathering 100% accurate data is not an easy task in the current situation and for better RO there is need of more research in coming days (13). There should also be a study about COVID 19 in children to completely know about pathogenesis of virus and so far COVID 19 disease research is mainly focused on adults and their research on children infected with COVID 19 is quite lower (22).

EPIDEMIC CURVE OF INFECTION

Epidemic curve can be defined as a statistical chart that provides visual representation in the shape of graphs to understand onset of a disease outbreak. Epidemic curve uses three zones that separately describe the knowledge about the outbreak disease which are increasing phase, plateau phase and declining phase.

- Increasing phase, different parameters affect this phase such as demographics of selected countries, difference in age of infected persons, response of health care systems to outspread of disease, and execution of preventative measures. Each country has its own ways to tackle the outbreak and because of that there may be complications about the pattern of pandemic. Still, it is assumed on the basis of different studies that this increasing phase for COVID 19 is between 3 to 4 weeks.
- Plateau phase, COVID 19 prevalence at this stage is steady. For COVID 19 this phase is between 2 to 3 weeks based on daily country reports.
- Decreasing phase, for this phase there are different reports however China report on this phase based on data of china is between 2 to 3 weeks (6).

COVID 19 MILD AND SEVERE DISEASES COURSES

COVID 19 disease caused by SARS-cov-2 has been observed to not stick to specific forms of infection and the course of infection varies from individual to other with elderly persons being infected with severe cases while young one develop a mild case. Along with that it has been observed that men are mostly infected with severe cases that may be attributed to the immune system weakness that may be due to obesity, other chronic diseases and hypersensitivity diseases and persons with severe infection also have shown more number or load of virus in their body as compared to mild cases. Another factor that plays a

role in mild and severe cases is smoking. Smoking leads to production of angiotensin converting enzyme 1(ACE2).ACE2 empowers SARA-cov-2 to take up to host cells (23).

PATHOPHYSIOLOGY

During pathogenesis coronaviruses mainly target and infect the respiratory tract as well as may also infect other crucial organs of the body such as kidneys. Pathogenesis begins after once the person inhales infected droplets with SARS-cov-2 produced by sneezing or coughing by infected symptomatic or non-symptomatic persons. These droplets may also settle down on surfaces and after touching these surfaces the virus sticks to hand and by touching hands to nose mouth or eyes leads to entrance of in the body and begins infection with ACE2 using as key receptor for attachment to begin infection (14).

So, after inhalation, the next step of pathogenesis is attachment done by ACE2 enzyme present on cells of organs such as lungs, kidneys, intestine, testis, and heart. The data regarding these receptors is present in the genome of virus and it produces S protein present on its surface that binds to the ACE2 receptor and attachment occurs. As ACE2 is also present in intestinal tract therefore the virus has also been found residing in faeces of infected individuals.it must be noted that ACE2 receptor is not present on immune cells (23).

So it is confirmed that pathogenesis begins with exposure of virus to mucus membranes present in mouth, nose, and eyes but respiratory tract is not the only way to give route to the virus for infection.as the ACE2 receptors are present in intestinal tract so contaminated food may also lead to infection and after that virus hides in faeces and contamination of drinking water with infected persons faeces also leads to infection with SARS-Cov-2 virus (24).

Once a pathway is given to the virus for entry into the body it mainly attacks the respiratory tract and travelling through the respiratory tract it reaches to the lung's alveoli. Alveoli also have ACE2 receptors. Once entering, alveoli virus attacks type 2 pneumocytes and attach itself to the receptors ACE2 present on the surface of type 2 pneumocyte. Attachment to the ACE2 receptor is done with the help of S protein present on the surface of the virus that has increased ability to bind with these ACE2 receptors. After attachment to the host cell such as type 2 pneumocytes the virus gets engulfed by the host cell by a process known as endocytosis in which the whole virus enters the cytoplasm of the host cell. In the cytoplasm of the host cell there are enzymes called lysozyme that attack the virus as part of immunity which leads to breakdown of virus lipid membrane and viral genome gets exposed to the cytoplasm. Now the viral genome that is single stranded RNA positive sense uses the host ribosome to produce polyproteins directly using the genome as mRNA. The polyproteins produced will act as a structural framework for new viruses. Using host cell RNA dependent RNA polymerase these polyproteins replicate themselves so that the viral loads increase in the host cell. Then these polyproteins utilize host cell enzymes like proteinases to break down the polyproteins into separated proteins to make structural proteins of the virus. Now these structural proteins are assembled in the membrane of the host and a high load of newly formed viruses is produced that is released into the neighbouring cells (7).

SARS-Cov-2 virus uses two ways for entry onto the host cell which may be endosomal or non-endosomal or sometimes may combine these both pathways. Just before attachment to the receptor there happens a molecular change in S1 domain of S protein of virus that enhances attachment of virus to the host cell. There are certain factors that enhances attachment of virus to the host cell receptor that may include presence of decreased pH around cellular surroundings, presence of specific proteases like cathepsin-L, airway trypsin like proteases and transmembrane proteases.it has been noted that the SARS-cov-2 causes self-destruction of cells called apoptosis in in cells including mucosal cells, neuronal dendritic cells, kidney tubular cells and immune cells that makes a decreased response of immunity to the virus (1, 16).

REPLICATION STRATEGY

Studies based on coronaviruses have shown that these positive sense single stranded corona viruses do contrast the way of replication then previously studied positive sense viruses. The major details of their replication strategy are given below:

- The way by which genomic information is expressed is arbitrated by multiple sub genomic RNA sequences present at 3' end of the sequence that moves inward to the 5' ends of the sequence.
- Different mRNA copies are formed with each producing separate protein.
- The produced protein size relates to the potential of 5' end of sequence (17).

INCUBATION PERIOD

Incubation period is the time required by pathogen to infect or produce symptoms and incubation period for the SARS-cov-2 ranges between 2 to 7 days. This incubation period may increase to 10 days in some patients (14).

TRANSMISSION

Despite of the fact that corona viruses reside in animals only and are zoonotic means transmitted via animals to humans but once infected human transmission mainly occurs between humans just like SAR cov 1 and MERS-Cov (6). When an infected person coughs it produces about 3000 droplets and these droplets are the major way of transmission (7).

HUMAN TO HUMAN TRANSMISSION

The biggest way of transmission of virus is by infected humans. Once a person gets infected it contains a high load of virus in its respiratory tract and when the person coughs or sneezes it releases the viral load into the air in the form of droplets. Now any healthy person who inhales these droplets gets exposed to the virus. Also, droplets settle down on objects and touching these contaminated objects transfer to the hands. Now touching these contaminated hands to mouth, nose or even eyes lead to transfer of virus to the body. There is also some proof of the virus being transferred through oral faecal route as the ACE2 receptors are present in the colon. Some routes of transmission between humans like breastfeeding, sweat, and semen are under study and research (1).

ANIMAL TO HUMAN TRANSMISSION

Humans can also get infected through corona viruses through animals as the corona viruses use animals as their primary hosts and are zoonotic in nature. It is also believed that the first case of COVID 29 occurred due to transfer of pathogens from bats (5). Not only live animals or their direct contact transfers the disease but also use of their uncooked meat, use of their raw milk or consumption of their urine leads to transmission of virus from animals to humans (1).

TRANSMISSION THROUGH FOMITE

The SARS-Cov-2 virus has the ability to survive for hours and may be even more on surfaces depending on conditions so there is equal chance of spreading of this virus through use of contaminated objects like cloths, utensils, steel objects etc (25).

TRANSMISSION THROUGH ENVIRONMENTAL FACTORS

Environmental factors like temperature, humidity and sunlight also influence spread of corona viruses. In different environmental conditions the virus respond differently. The records suggest that the virus has the lowest rate of spread in African countries where there is mostly high temperature while in cold regions the virus has a quick outspread and in winter season the transmission rate increased even more (25).

HUMAN TO ANIMAL TRANSMISSION

There is not enough research about transmission of virus from humans to animals but there has been a case reported in the United States of America where a tigers was infected from a non-symptomatic zookeeper which makes the situation very important (1).

FAECAL TRANSMISSION

Currently research is being done about faecal transmission of virus. It has been proved that the virus infects the gastrointestinal tract as faecal samples were positive for SARS-cov-2 and also live SARS-cov-2 virus has been detected in stool samples according to which we can say that the virus can also transmit through faecal oral route (6).

RISK FACTORS

There are factors that make virus more vulnerable such as people with age more than 70 are more at risk of developing severe infection while young people develop mostly mild forms of infection. Also people with obesity and other chronic diseases also are more at risk to develop severe forms of COVID 19 disease. It is also noted that there are more men being positive for COVID 19 than women (23).

However main risk factors for COVID 19 are:

- Gender difference with males more at risk of infection (23)
- Difference in age with elderly people being more at risk to develop disease (23)
- People with previously chronic disease are also at more risk (23).
- Smokers are also at more risk to get infection (20)

SYMPTOMS

The principal clinical manifestations of COVID 19 disease are respiratory in nature that is related with high temperature and loose motion (12). According to the research more than 97% of people infected with COVID 19 start showing symptoms within 11 days of infection (25). Symptoms of infected persons also vary from one person to other with some even not showing any kind of symptoms. Temperature in infected persons (not all) slight cough, pain in throat, headache, tiredness, and difficulty in breathing are most common symptoms of COVID 19 disease. In some patients there is also a unique symptom of conjunctivitis. So these symptoms except for few most of them are not easy to distinguish from other infections of the respiratory tract. There have been some cases where the patient infected with COVID 19 develops pneumonia, failure of respiration and even death within a week (8). However, this is not specific for all patients and most of the patients that died due to COVID 19 had a gap of 6 to 41 days from onset of symptoms to death. This period also depends on age and immunity of the patient (7).

It has been also studied that approximately 80% of patients infected with SARS-cov-2 does not show any kind of symptoms (5). The Centre for disease control and prevention (CDC) has said that the way of disease varies from symptomatic to non-symptomatic patients and therefore the disease is grouped into 3 types including mild, moderate, and severe type. However, the major symptoms of COVID 19 disease are high temperature, a dry cough, and pain in throat, problem in speaking and difficulty in breathing. While the minor symptoms include runny nose, headache, pain in throat, loose motion and vomiting (14).

DIAGNOSIS

Basic diagnosis of COVID 19 is usually done on the basis of symptoms, recent travel history and chest x rays. As the persons infected with COVID 19 show various types of symptoms but not all of these symptoms are present in every patient also these symptoms resemble to other common respiratory infections caused by other viruses hence it is suggested that there should be detailed and exact clinical examination needed in advance of declaring patient with COVID 19 (5).

Best way to diagnose COVID 19 patients is using PCR testing from samples taken from the nose of patients. There have been many false reports of PCR test of nasal swabs so to overcome that other diagnostic techniques must be used that include laboratory examinations, molecular tests and chest x-rays (25).

To Diagnose COVID 19 following techniques can be used:

- Reverse transcription polymerase chain reaction (11)
- Enzyme-Linked immunosorbent Assay (ELISA) (11)
- Immune chromatography (11)
- Genome sequencing (11)

- Imaging, chest x ray, chest CT scan, ultrasound (9)
- Physical examinations, symptoms review and history of patient (8)

NONSPECIFIC EXAMINATIONS

Nonspecific examination of COVID 19 shows that more than 80% of patients infected with COVID 19 have decreased number of white blood cells and other lymphocytes where both CD4 and CD8 cells decrease in number along with a decrease in number of blood platelets along with that there is increase in sedimentation rate of red blood cells. Some researchers have also said that in COVID 19 ratio between neutrophil and lymphocyte also changes (11).

BLOOD AND CHEMICAL TESTS

Blood tests as studied shows a remarkable change in number and ratio of blood cells while biochemical tests of serum of patient infected with COVID 19 suggest increase in serum aspartate transaminase (AST), lactate dehydrogenase (LDH), prolactin, bilirubin alanine aminotransferase (ALT) furthermore there is increased levels of inflammatory markers like C reactive proteins (CRP) and ferritin (14).

MOLECULAR AND SEROLOGICAL TESTS

Molecular diagnostic approach includes quantitative reverse transcriptase polymerase chain reaction suggested by CDC to identify the pathogen and study viral genome acquired from samples of patients. This method generates results within 4 to 6 hours and is a sensitive method and is being used widely throughout the world laboratories.

There are also serological tests available to detect antibodies produced against pathogenic virus of COVID 19 and antigens present in blood samples of patients that are ELISA (enzyme linked immunosorbent assay) and rapid diagnostic tests (RTD). Structural proteins of SARS-cov-2 that act as antigens are N and S that can be detected with the help of sandwich ELISA (14).

TREATMENT

There is no specific treatment that can cure COVID 19 that is now a serious world pandemic and therefore the focus is to overcome this pandemic to provide supportive treatment and controlling symptoms caused by the virus and making sure to prevent exposure to the virus for healthy ones. Most of the patients infected with this disease normally recover on their own and before they recover they are advised to remain alone in a specific room being separated from other individuals at least for 7 days (7). This is because so far not any single has been approved that specifically treat this pandemic and treatment centres are treating infected patients with supportive therapy and reducing symptoms only (4). First step to treat coronavirus infected persons is to keep them isolated from healthy individuals and then giving them supportive therapy (8).

When a person infected from COVID 19 gets recovered then his plasma and antibodies produced by his immune system can also be used to treat severely infected individuals (4). There are certain drugs that are under study and research before being approved and commercially available that include chloroquine, remdesivir, arbidol and favipiravir. Their effectiveness and wellbeing is still yet to be known (14). Among supportive therapy specially for severely ill individuals' involuntary ventilation of oxygen is a major way to control severity of infection. It is done in two ways, one is an invasive method in which a narrow tube is planted in trachea through the nose or mouth and the other way is non-invasive that uses a cover connected to an oxygen cylinder and provides oxygen to the infected person through mouth and nose (5) (25).

PREVENTION

Even though the World health organisation has provided instructions to prevent reappearance of any new coronavirus strain as of 2004 but the execution of those instructions has been very poor, not enough because of this world has faced MERS in 2012 and SARS-cov-2 in 2019. The major instruction that has been neglected is to detect any infection as soon as possible to stop further spread of the infection specially spread through international travelling that leads to more severe situation, to build out a road map by every single country

to manage and detect any new infectious pathogen, making sure new discoveries reach to every country and helping every country to boost up their efforts to get protection against any new infection (12).

Individual prevention can be done by (26):

- observation and personal hygiene (26)
- sterilization of food (26)
- isolation of infected individuals (26)
- maintaining a social distance (26)
- keeping away from gatherings (26)
- must cover nose and mouth with a face mask (26)
- washing hands regularly with soap and water or hand sanitizers (26)
- get vaccinated (7).

CONCLUSION

Before the 2019 outbreak of the virus there was little known about the virus and its ability to cause a pandemic. Still now a lot of work must be done to prevent another outbreak. For now, there is no certain treatment of the virus and medication is focused to decrease symptoms as much as possible however different pharmaceutical companies have come forward with vaccines which at present are looking helpful but there still need to be done a lot of research by the responsible authorities and as far as concern of the individuals social distancing, wearing mask, avoiding gathering etc to prevent from being infected.

References:

1. Altaf R, Iftikhar A, Haq R, Zahoor B, Zaini M, Khadeer M. History, Epidemiology, Vaccine and Transmission of Coronavirus Disease 2019 (COVID-19): A Quick Review. *Life Res.* 2021;4(3):1.
2. Chvatal-Medina M, Mendez-Cortina Y, Patiño PJ, Velilla PA, Rugeles MT. Antibody Responses in COVID-19: A Review. *Front Immunol.* 2021;12(4):1–14.
3. Wolff D, Nee S, Hickey NS, Marscholke M. Risk factors for Covid-19 severity and fatality: a structured literature review. *Infection [Internet].* 2021;49(1):15–28.
4. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol.* 2020;92(4):418–23.
5. Abebe EC, Dejenie TA, Shiferaw MY, Malik T. The newly emerged COVID-19 disease: A systemic review. *Virol J.* 2020;17(1):1–8.
6. Bulut C, Kato Y. Epidemiology of covid-19. *Turkish J Med Sci.* 2020;50(SI-1):563–70.
7. Hussain A, Kaler J, Tabrez E, Tabrez S, Tabrez SSM. Novel COVID-19: A Comprehensive Review of Transmission, Manifestation, and Pathogenesis. *Cureus.* 2020;12(5):1–14.
8. Bhatt T, Kumar V, Pande S, Malik R, Khamparia A, Gupta D. A Review on COVID-19. *Stud Comput Intell.* 2021;924(4):25–42.
9. Jamil S, Mark N, Carlos G, Dela Cruz CS, Gross JE, Pasnick S. Diagnosis and management of COVID-19 disease. *Am J Respir Crit Care Med.* 2020;201(10):19–22.
10. Lella KK, PJA A. A literature review on COVID-19 disease diagnosis from respiratory sound data. *AIMS Bioeng.* 2021;8(2):140–53.
11. Oliveira BA, de Oliveira LC, Sabino EC, Okay TS. SARS-CoV-2 and the COVID-19 disease: A mini review on diagnostic methods. *Rev Inst Med Trop Sao Paulo.* 2020;62(5):1–8.
12. Docea AO, Tsatsakis A, Albulescu D, Cristea O, Zlatian O, Vinceti M, et al. A new threat from an old enemy: Re-emergence of coronavirus (Review). *Int J Mol Med.* 2020;45(6):1631–43.
13. He F, Deng Y, Li W. Coronavirus disease 2019: What we know? *J Med Virol.* 2020;92(7):719–25.
14. Attia YA, El-Saadony MT, Swelum AA, Qattan SYA, Al-qurashi AD, Asiry KA. COVID-19: pathogenesis, advances in treatment and vaccine development and environmental impact—an updated review. *Environ Sci Pollut Res.* 2021;28(18):22241–64.
15. Al-Osail AM, Al-Wazzah MJ. The history and epidemiology of Middle East respiratory syndrome corona virus. *Multidiscip Respir Med.* 2017;12(1):1–6.
16. Olwenyi OA, Dyavar SR, Acharya A, Podany AT, Fletcher C V., Ng CL. Immuno-epidemiology and pathophysiology of coronavirus disease 2019 (COVID-19). *J Mol Med.* 2020;98(10):1369–83.
17. Siddell S, Wege H, ter Meulen V. The structure and replication of coronaviruses. *Curr Top Microbiol Immunol.* 1982;99:131–63.
18. Spaan W, Cavanagh D, Horzinek MC. Coronaviruses: Structure and genome expression. *J Gen Virol.*

- 1988;69(12):2939–52.
19. Informatics M, Imaging B. 1, 2, 3 ; 2020;19.
20. Jordan RE, Adab P, Cheng KK. Covid-19: Risk factors for severe disease and death. *BMJ* [Internet]. 2020;368(3):1–2.
21. Lotfi M, Hamblin MR, Rezaei N. COVID-19: Transmission, prevention, and potential therapeutic opportunities. *Clin Chim Acta*. 2020;508(4):254–66.
22. Bhumbra S, Malin S, Kirkpatrick L, Khaitan A, John CC, Rowan CM. Clinical Features of Critical Coronavirus Disease 2019 in Children*. *Pediatr Crit Care Med*. 2020;63(4):E948–53.
23. Brodin P. Immune determinants of COVID-19 disease presentation and severity. *Nat Med* [Internet]. 2021;27(1):28–33.
24. Amesty MA, Alió del Barrio JL, Alió JL. COVID-19 Disease and Ophthalmology: An Update. *Ophthalmol Ther*. 2020;9(3):415–26.
25. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA - J Am Med Assoc*. 2020;324(8):782–93.
26. Arefi MF, Poursadeqiyan M. A review of studies on the COVID-19 epidemic crisis disease with a preventive approach. *Work*. 2020;66(4):717–29.

