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Review Article

COVID-19: An Emerging Rapidly Evolving Situation

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Abstract Coronaviruses are large group of enveloped viruses with unsegmented, single-stranded, positive-sense RNA as genetic material. These are collection related RNA viruses that cause diseases of economically important vertebrate viz. mammals and birds. In humans, these viruses cause respiratory tract infections that can range from asymptomatic to life threatening. The asymptomatic disease include very similar to some cases of the common cold, while other deadly varieties can cause SARS, MERS, and COVID-19. The SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) are zoonotic origin and extremely pathogenic coronaviruses that can cause localized and worldwide outbreak. The novel Coronaviruses, COVID-19 posses a unique morphology. The outer surface of the virus bearing surface spike and reveled like crown hence being named corona virus. The mode of replication of the virus is very unique as it replicate through the generation of nested set of viral mRNA. The HCoV (Human coronavirus) cause respiratory complication with asymptomatic to life threatening outcomes. From the past 15 years we have witnessed appearance of two zoonotic, extremely pathogenic human corona viruses the: SARS-CoV and MERS-CoV.

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INTRODUCTION

Corona viruses are a group of related RNA viruses that cause diseases in mammals and birds. In humans, these viruses cause respiratory tract infections that can range from asymptomatic to life threatening. The asymptomatic infections are very much similar to the common cold, which is caused some influenza virus mainly rhinoviruses. The more severe infection causes SARS, MERS, and COVID-19. In the end month of 2019, a chain of respiratory problems, diarrhea and pneumonia cases of mysterious cause appeared in Wuhan, China (Lu *et al.*, 2020). After few weeks in January, 2020 the genomic analysis of the lower respiratory tract exudates of the observed pneumonia patient was carried out and a new strain of corona virus detected. The novel isolated virus was identified as SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) (Huang *et al.*, 2020). On February 11th, 2020, the WHO (World Health Organization) renamed the virus SARS-CoV-2 as "COVID-19". By March 11th, 2020 the infection speeded and spread in 114 countries with more than 118,000 cases and 4000 death, the WHO declared the pandemic status (WHO, 2020). Globally, as of 9:11am CEST, 6 June 2020, there have been 6,612,301 confirmed cases of COVID-19, including 391,161 deaths, reported to WHO from 213 *Countries* and Territories (Phan, 2020). The novel corona virus isolated in Wuhan has been recognized as a new strain of Betacoronavirus from group 2B with approximately 70% hereditary resemblance to the SARS-CoV. The SARS-CoV-2 virus has 96% resemblance to a bat coronavirus, so it is generally supposed to instigate from bats. A Similar occurrence has been reported with the SARS-CoV (severe acute respiratory syndrome coronavirus) in the year 2002 and MERS-CoV (Middle East respiratory syndrome coronavirus) in the year 2012 respectively. 2019-nCoV is the third coronavirus to emerge in the human population in the past two decades a materialization that has put global public health on high alert (Shrikushra *et al.*, 2020). This assessment aim to summarize all available findings on the epidemiology, clinical features, diagnosis, management, and prevention of COVID-19.

CORONA VIRUS

Coronaviruses constitute the subfamily *Orthocoronavirinae*, in the family *Coronaviridae*, order *Nidovirales*, and realm *Riboviria* (Cohen,2020; Eschiner, 2020). They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry (Fenner's, 2017). The novel corona virus is one of

the largest RNA viruses with genome size range from ~26 to 32 kilobases (Fan *et al.,* 2019). They have distinctive club-shaped spikes that are projected from the outer envelope. In electron micrographs it forms an image redolent of the solar corona, hence they named as corona virus (de Groot *et al.,* 2011). The appearance of this virus viz. origin, transmission among human is still mystifying. An increasing number of cases appear to have resulted from human-to-human transmission (ICTV, 2010). Coronaviruses are huge, approximately sphere-shaped, particle with bulging surface spikes (Cherry *et al.,* 2017). The approx diameter of the virus particles is roughly 125 nm. The diameter of the envelope is about 85 nm and the lengths of the spikes are 20 nm. The outer covering of the virus is opaque shell shown in electron micrograph (Woo *et al.,* 2010; Almeida *et al.,* 1968). The viral genome is wrapped in double lipid layer forming envelop (E), the membrane (M), and spike (S) structural proteins are anchored (Almeida *et al.,* 1968). The proportion of E: S: M in the lipid bilayer is roughly 1:20:300 (GoldSmith *et al.,* 2004).

The surface spikes are helping the virus to interact and attach with the host cell receptor, a single coronaviurus particle bear roughly 74 spikes (Neuman *et al.,* 2006). The beta coronavirus sub group A, member of coronavirus family have comparatively shorter surface spike and called (HE) hemagglutinin esterase (Fehr and Perlman, 2015). The surface spikes of coronavirus are homotrimers of the S protein, which is composed of two subunit S1 and S2 respectively. The homotrimeric S protein is a class I fusion protein which mediates the receptor binding and membrane fusion between the virion and host cell. During the attachment and invasion process the two subunit of surface protein perform separate work. The first subunit S1 forms the head of the spike and has the receptor binding domain. While the other subunit S2 forms the stem which anchors the spike. The two subunit together involved in the protease activation enables fusion of the virion. The morphology and the structure of the virion is maintained E and M protein found in envelop and membrane respectively (Lai and Cavanagh, 1997).

The viral nucleocapsid, which is made up with several copies of the nucleocapsid (N) protein, enclosed the positive-sense single-stranded RNA infectious genome in a unbroken beads-on-a-string type conformation (Cavanagh *et al.,* 2001; Neumann *et al.,* 2011). The nucleocapsid is protected from any unfavorable condition or enzymatic action by membrane protein and lipid bi-layer envelop. (Chang *et al.,* 2014). The structure of coronovirus depicted in figure 1.

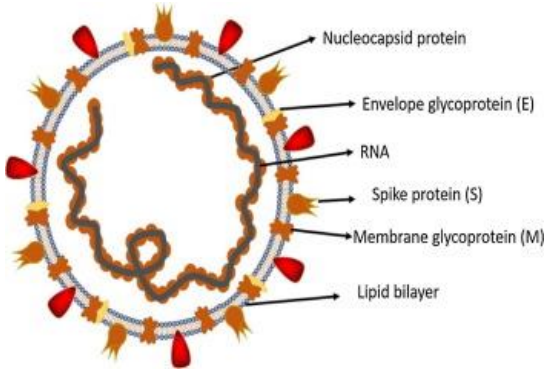

Figure 1: Coronavirus structure (Neumann *et al.,* 2011)

There are four genera of CoVs: (I) -coronavirus (alphaCoV), (II) -coronavirus (betaCoV) probably present in bats and rodents, while (III) -coronavirus (deltaCoV), and (IV) -coronavirus (gammaCoV) probably represent avian species (Lu et *al.,* 2020a; Muhammad *et al.,* 2020). The virus has an innate and zoonotic (from animal) origin. The two possible pathway that can possibly explicate the derivation of SARS-CoV2 are Natural selection in an animal host before zoonotic transfer, and natural selection in humans following zoonotic transfer (Cavanagh *et al.,* 2001; Chang *et al.,* 2014). Clinical features and risk factors are highly variable, making the clinical severity range from mild to severe (Muhammad *et al.,* 2020). Understanding of COVID-19 is still on-going.

CLINICAL FETURES

Cold- or flu-like symptoms usually set in from 2–14 days after a coronavirus infection and are typically mild. Though, symptom varies from person-to-person, and directly proportional to immunity of the host. Some mutant of the virus may be cause severe infection to life threatening. The symptoms as common as common cold may include: Sneezing, Runny nose, dry cough, diarrhea, high Fever, Sore Throat, breathing problem, hypoxia etc. (Shrikushra *et al.,* 2020). The human coronaviruses is difficult to cultivate in the laboratory unlike the rhinovirus. This makes it hard to judge the impact of the coronavirus on the global economies and community health. There is no vaccine for the disease the prophylaxis of the disease includes only social distancing, wearing mask, quarantine, self isolation. The treatment includes self care, and over the counter medication. People can take several steps, including: resting at home, drinking plenty of water, avoid respiratory distress such as smoking and smoky area, eating nutritious and health diet etc.

The infection can be prevented by frequent hand washing, casing mouth and nose when coughing and sneezing, carefully cooking meat and eggs. keep away from close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing (Shrikushra *et al.,* 2020).

EPIDEMIOLOGY

In December 2019, a sudden outbreak of 54 cases of viral pneumonia with respiratory distress was reported in Wuhan, China caused by unknown microorganism. Later on the microorganism responsible for this pneumonia was recognized as novel coronavirus of the family Coronaviridae. The novel coronavirus was renamed as COVID-19 by WHO. Since the outbreak of the disease the infection increased exponentially and has stretched all over the globe in more than 196 countries. The WHO has confirmed a Public Health Emergency of International apprehension due to the outburst of COVID-19 (Yin and Wunderink 2018). The virus is exceedingly infectious and can cause human-to-human transmission. In every 24 hour, cases of COVID-19 amplify a number of folds and transmitted on the theory of chain reaction. The WHO is monitoring the SARS-CoV-2 spread very closely via a global surveillance system. The current situation demands the enforcement of strict laws which would help in inhibiting the further spread of COVID-19. The virus chain can be split via social distancing, avoid public gathering, covering face while coughing and sneezing, restriction of international travel or national travel to the affected countries or states are the significant ways to minimize the transmission of SARS-CoV-2. The government should enforcing law and order and tie up with the local authorities to minimize the transmission rate and disease management during this pandemic. Public awareness, social distancing, and sterilization must be maintained to neutralize the viral infection, especially in major hot spots (Hugan *et al.* 1988). As of *July* 31, *2020*, *the* outbreak of the *coronavirus* disease (*COVID*-19) have been established in around 210 *countries* or territories with total number of positive case worldwide is 17,512,049, and death of 677,543 has been reported (WHO,2020). The leading countries of coronavirus (COVID-19) cases worldwide as of July 31, 2020 depicted in figure2.

PATHOPHYSIOLOGY

The novel coronavirus disease (COVID-19) is caused by SARS-CoV2 and represent the etiology of a potentially fatal disease that is of immense worldwide public health concern. The data recorded from the Wuhan, China has revealed that the large population of the infected people had a history of traveling to the wet animal market in Wuhan city, suggested that the virus likely have the zoonotic origin of COVID-19. Human-to-human spread of COVID-19 infection led to great challenge to cope up with the disease and the isolation of confirmed patients is very mandatory. Extensive actions to reduce human-to-human spread of COVID-19 have been implemented to manage the existing pandemic. Exceptional awareness and efforts are enforced to guard or reduce the spread infection in vulnerable populations including elderly people (Above 60 years) children (below 10 years) and health care providers (Knapp, 2020; Hamne and Procknow, 1966).

Coronaviruses primarily infect the upper respiratory and gastrointestinal tract of mammals and birds. Four to five different currently known strains of coronaviruses infect humans. The most known human coronavirus, SARS-CoV which causes SARS, has a distinctive way of pathogenesis because it affects both upper and lower

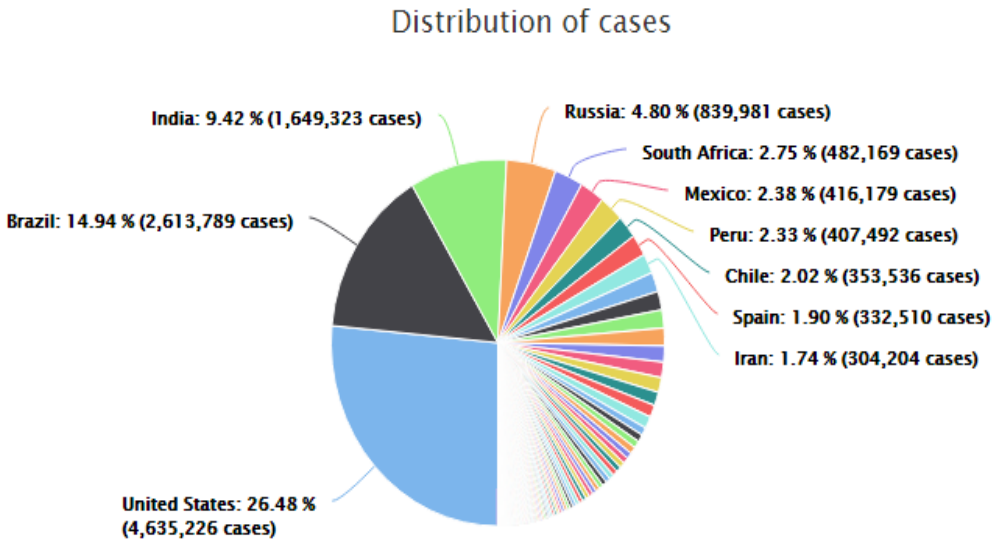

Figure 2: Distribution of coronavirus (COVID-19) cases worldwide as of July 31, 2020, 11:49 GMT by country (https://www.worldometers.info/coronavirus/)

respiratory tract and can also cause gastroenteritis. Coronaviruses are understood to cause a considerable proportion of all common colds in human. Coronaviruses cause common colds in humans mainly in the winter and spring seasons (Li *et al.,* 2005; Almeida and Tyrrel, 1967). The consequence and financial crash of coronaviruses as causative agents of the common cold are hard to evaluate because, human coronaviruses are not easy to grow in the laboratory unlike rhinoviruses (McIthos *et al.,* 1967). These viruses infect a variety of mammals and birds. The exact numbers of human isolates are not known as many cannot be grown in culture. In humans, they mainly cause respiratory illness including SARS, occasionally enteric infection mostly in infants <12 months and rarely involvement of nervous system (McIthos *et al.,* 1967a). Coronaviruses also threat for farming industry, they cause a verity of diseases in farm animals as well as in domesticated pets. Porcine coronavirus which cause transmissible gastroenteritis (TGE) and Bovine coronavirus both cause diarrhea in young animals are economically important coronaviruses of farming industry (Times, 1967). Generally, Feline enteric coronavirus a pathogen clinically non significant but spontaneous mutation of this virus can result in feline infectious peritonitis (FIP), i.e. a potentially disease associated with high mortality. There are two types of canine coronavirus (CCoV), one that causes respiratory disease and another that has been found to cause mild gastrointestinal disease (Times, 1967). Mouse hepatitis virus (MHV) is a member of coronavirus that causes an EMI (epidemic murine illness) with great mortality rate, particularly amongst colonies of laboratory mice. The MHV had been the best studied coronavirus both *in vitro* and *in vivo* as well as at the molecular pattern prior to the detection of SARS-CoV. Some mutants of MHV cause PDE (progressive demyelinating encephalitis) in mice which have been used as a murine model for MS (multiple sclerosis). Virologist interested in veterinary and zoonotic disease has been carried out considerable study and research on elucidating the viral pathogenesis and disease cycle of animal coronaviruses and their host (Myint, 1995).

HCoV-229E and HCoV-OC43 cause the mild illness including common cold, and a self-limiting upper respiratory tract infection. These infections can direct to a number of other co-related illnesses such as bronchitis, gastroenteritis, progressive demyelinating encephalitis, diarrhea, peritonitis, nasal obstruction, rhinorhea, sneezing, sore throat and cough. They can cause more severe lower respiratory tract infection, including pneumonia in infants, elderly and immune-compromised individuals. HCoV-229E is a common agent if coryza, whereas HCoV-OC43 is generally characterized by sore throats (Geller *et al.,* 2012). HCoV-NL63 causes laryngotracheitis (croup) and nonfatal upper and lower respiratory tract infections in children, elderly, and immune-compromised individuals. HCoV-HKU1 is another strain of SARS-CoV causes mild upper respiratory tract illness, the common cold, bronchiolitis, and pneumonia, with symptoms such as rhinorrhea, fever, cough, febrile seizure, and wheezing. More severe illness may occur in children, adults with underlying disease, the elderly, and may be associated with gastrointestinal illness (Corman *et al.,* 2014; Su *et al.,* 2016).

Laboratory Hazards

No infections have been reported till date. However, this may be an underestimate of the number of incidences as symptoms are nonspecific and self limiting (Zhu *et al.,* 2020).

- Source: Specimens of upper and lower respiratory tract.
- Primary Hazard: Aerosols and contact with stools.

Stability and Viability

- Drug Susceptibility: Specific coronavirus antiviral drug not available currently (Goldsmith *et al.,* 2004)
- Susceptibility to Disinfectants: Susceptible to 0.1% sodium hypochlorite, 0.1% organochlorine, 10% iodophore, 70% ethanol and 2% glutaraldehyde. Resistant to 0.04% quaternary ammonium compound and phenolics (Forni *et al.,* 2017).
- Physical Inactivation: Inactivation by UV light can be done by exposure to 1200 µJ/cm2 for 30 minutes (Forni *et al.,* 2017a).
- Survival outside Host: Survives up to six days in aqueous mediums and up to 3 hours on dry inanimate surfaces (Forni *et al.,* 2017).
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REPLICATION CYCLE

Entry of virion to host Cell

Any infection cycle begins here, in the initial phase the virion come in contact with the susceptible host cell and this is called landing. After landing the virion gains the entry to the host cell by multiphase process. The viral spike proteins attaches to its complementary host cell receptor by key –lock mechanism and the phenomenon known as viropexix. After interaction with the host cell an ATP driven protease of the host cell cleaves and activates the receptor-attached spike protein. The amount available protease in the host cell, allows the virus to enter the host cell by the process of endocytosis or by direct fusion of the viral envelop with the host cell membrane (Simmons *et al.,* 2013).

Genome translation

On entry into the host cell, the virion is uncoated, and its genome enters the cell cytoplasm. The

coronavirus RNA genome has unique features a 5′ methylated cap and a 3′ polyadenylated tail. Due to these modifications the coronavirus RNA genome easily attach to the host cell's ribosome for the process of translation and protein synthesis. The host cell ribosome start translating initial overlapping open reading frames ORF1a and ORF1b of the viral genome into two large overlapping polypeptides, pp1a smaller chain and pp1ab larger chain (Fehr and Perlman, 2015). The larger polyprotein pp1ab is formed due to result of a -1 ribosomal frame shift mutation caused by a slippery sequence (UUUAAAC) and a downstream RNA pseudoknot at the last part of open reading frame ORF1a (Sexton *et al.,* 2016). The ribosomal frameshift permit the uninterrupted translation of ORF1a followed by ORF1b (Fehr and Perlman, 2015). The polypeptides contain their own proteases, PLpro and 3CLpro, which slice the polypeptides at different specific sites. The cleavage of polypeptides pp1ab produced 16 nonstructural proteins (nsp1 to nsp16). The Product proteins comprise different replication proteins such as RNA-dependent RNA polymerase (nsp12), RNA helicase (nsp13), and exoribonuclease (nsp14) (Fehr and Perlman, 2015).

Replicase-transcriptase

A number of the nonstructural proteins combine to form a multi-protein replicase-transcriptase complex. The chief replicase-transcriptase protein is the RNA-dependent RNA polymerase (RdRp). The RdRp mainly involved in the replication and transcription of RNA from Parent RNA template. The other nonstructural proteins in the complex support the replication and transcription process. The exoribonuclease nonstructural protein provides extra conformity to replication by providing a proofreading job which the RNA-dependent RNA polymerase lacks (Payne, 2017).

***Replication*–** One of the main functions of the replicase-transcriptase complex is to reproduce the viral genome. RdRp directly catalyze on viral positive-sense genomic RNA and mediates the synthesis of negative-sense genomic RNA. In the second cycle now positive sense viral RNA synthesized from the negative-sense genomic RNA and the cycle continue (Fehr and Perlman, 2015).

***Transcriptio* –** The next function of replicase-transcriptase complex is to transcribe the viral genome and produce viral mRNA for protein synthesis. RdRp directly acts on negative-sense subgenomic RNA molecules from the positive-sense genomic RNA. This process mainly focused on transcription of the negative-sense subgenomic RNA molecules to their corresponding positive-sense mRNAs (Fehr and Perlman, 2015). The newly synthesized sub genomic mRNAs form a "nested set" which have a common 5'-head and partially duplicate 3'-end (Su *et al.,* 2016).

***Recombination* –** The complex also provide the platform for the genetic recombination when at least two genome are present in the same infected cell (Su *et al.,* 2016). Recombination of the genetic material appears to be a main dynamic power in determining genetic variability within a coronavirus species. These genetic recombination produce mutant coronavirus and these new species are capable to cause cross infection to another host. The emergence of novel coronavirus may be result of this genetic recombination and mutation of wild strain (Fehr and Perlman, 2015). The precise mechanism of recombination in coronaviruses is still imprecise, but probably it involves template switching during genome replication or recombination (Fehr and Perlman, 2015).

Assembly and release

The newly synthesized positive-sense genomic RNA produced after replication in the host cell becomes the genome of the progeny virion. The mRNAs produced after transcription undergoes translational process to synthesized structural proteins and other accessory proteins by using host ribosome (Fehr and Perlman, 2015). mRNA translation occurs inside the endoplasmic reticulum. The viral structural proteins viz. S (spike), E (envelope), and M (membrane) move alongside the secretary pathway into the Golgi apparatus compartment. M proteins play important role in virion packaging it assist most protein-protein interactions essentially required for the assembly of viruses following its binding to the nucleocapsid. After complete assembly and maturation the progeny viruses are then released from the host cell by exocytosis through secretory vesicles. Once released the viruses can infect other new host cell and repeate again the same cycle (Masters, 2006). The replication cycle of coronavirus is depicted in figure 3.

TRANSMISSION

Infected carriers are capable of disseminate viruses into the environment. The spikes protein interacts with its complementary cell receptors play essential role in virus propagation. The virus shows tissue tropism which directs the spikes protein to bind with specific cell receptors and determining its rate of replication and multiplication (Dacaro *et al.,* 2011; Dacaro *et al.,* 2011a). Coronaviruses mainly target epithelial cells. The mode of transmission of coronavirus depends on its species. They are mainly transmitted either by direct contact, aerosols, fomite and fecal-oral route from one host to another host (Li *et al.,* 2005). The affinity of infection of coronavirus varies species to species.

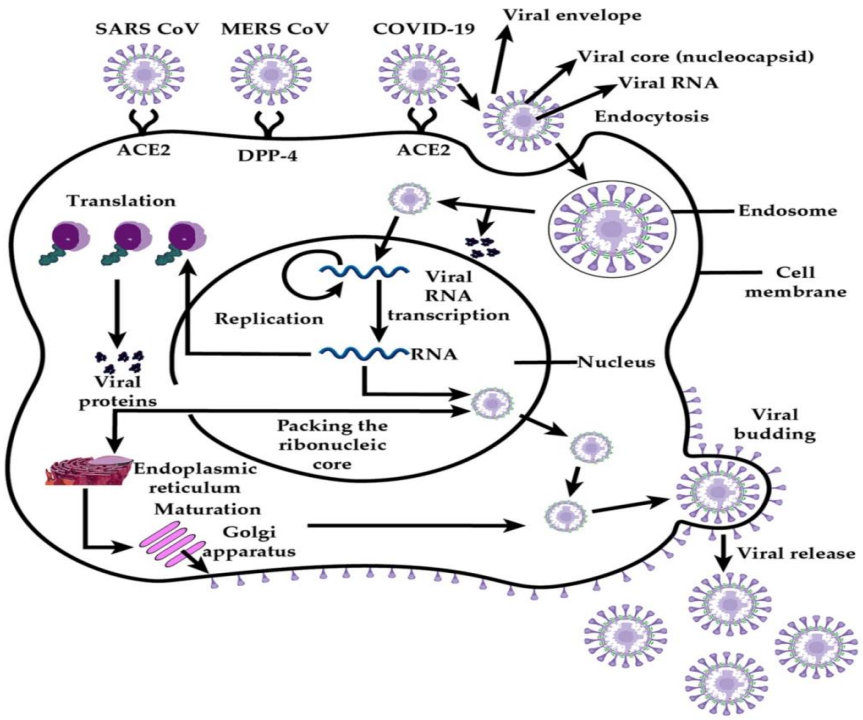

Figure 3: Replication of corona virus (Cui et al., 2019).

The animal coronavirus generally infect intestinal epithelium cells of the digestive tract. On the other hand human coronavirus have high affinity towards the respiratory epithelium and infect the upper and lower respiratory tract significantly. The SARS coronavirus, infects the respiratory tract from the carrier droplet or aerosolized particle present in atmosphere (Wertheim *et al.,* 2013). The angiotensin-converting enzyme 2 (ACE2) present in the epithelium cells of lungs have high affinity with viral spikes protein, which assist binding to receptor cells (Woo *et al.,* 2012). While on the other side TGEV (Transmissible gastroenteritis coronavirus) infects, via a fecal-oral route. The binding of viral spikes with host cell receptor is mediated by alanine aminopeptidase (APN) receptor present in the epithelial cells of pig digestive tract (Fehr and Perlman, 2015; Forni *et al.,* 2017). They are transmitted by aerosols of respiratory secretions, by the fecal-oral route, and by mechanical transmission. Most virus growth occurs in epithelial cells. Occasionally the liver, kidneys, heart or eyes may be infected, as well as other cell types such as macrophages (Huynh *et al.,* 2012). The incubation period of the virus is 2-14 days or depending on the host immunity. The possible ways of transmission of the virus is mainly Human-to-human transmission which include infectious droplets, sneezing, aerosols or through contaminated surface or utensils.

Role of Spike Proteins

- They induce neutralizing antibody.
- They are important in relating host cell tropism.
- Hemagglutination.
- They mediate the cell to cell or cell to viral fusion by the interaction between viral envelope and the specific receptor of host cell membrane.

PROPHYLAXIS AND TREATMENT

The coronavirus is highly infectious and its doubling rate is very high. The only way to reduce its infection from spreading is self isolation, social distancing, sanitization and covering mouth and nose while coughing and sneezing. Also implement the guidelines imposed by government or local public health agency (Shrikushra *et al.,* 2020; Neumann *et al.,* 2011). To prevent the spread of COVID-19:

- Clean hands with soap and water frequently also use alcohol-based hand rub.
- Maintain social distance approximately 6 ft from anyone you see the symptoms such as sneezing or coughing.
- Avoid touching face especially mouthing, nosing and eyes.
- Use of face cover in public place or while cough or sneeze.
- Stay at home if a person unwell. If reported with fever, cough and respiratory distress, immediately look for medical care.
- Strictly implement the guidelines given by your public health authority.
- Avoiding unnecessary visits to hospitals, nursing homes or health care system to function more effectively.

There are no specific vaccines or antiviral drugs available to stop or cure human coronavirus infection. Treatment is only compassionate to minimize the health risk. A number of antivirial

targets have been acknowledged such as receptor blocking viral proteases, polymerases, and ingress proteins. Currently drugs are under research and development which targets mainly to stop the viral replication in the host cell. A massive research and study under progress to develop vaccine against corona virus is still challenge due to its pleomorphism which varied according to different geographical location(Fehr and Perlman, 2015; Huynh *et al.*, 2012).

CONCLUSION

The Coronaviruses belongs to family coronaviridae may infect large population from animals to human. The virus cause respiratory disease from mild to severe including death. In the past decade two form of coronavirus disease already been faced by human civilization including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Recently, another coronavirus species (SARS-CoV-2) been reported in Wuhan, China in December 2019 and WHO named this as COVID-19.

Due to its high infecting rate and affecting more than 200 countries worldwide, WHO declared it pandemic. The virus can infect any age of people but the children less than 10 years and elder more than 60 years are at greater risk. The symptoms of coronavirus are unlike to common cold which includes fever, cough, sneezing and bodyache in mild infection, but may be life threatening if it severely infect the lungs causing hypoxia. Other sign may include headache, nasal stiffness, sore throat, conjuctivities, diarrhea, loss of taste or smell, skin rashes etc.

In starting of the infection is begins like common cold. Some may recover within few days in mild infection but they are potential reservoirs and shed virus in their droplets. The disease spreads silently from human to human through fomites or aerosols from mouth and nose which are produced during cough, sneeze or normal conversation. The droplets are heavy and cannot travel far away and fall on grounds, table, or any other objects are potential reservoirs and can transmit disease to healthy person. The transmission of the virus can be prevented by maintaining social distance (approximately 6ft), self isolation, frequently washing hand with soap and water, avoid to touch mouth, nose and eyes and covering mouth while cough and sneeze. WHO does not recommend self medication for COVID-19, but some traditional or home remedies may provide comfort and improve the condition. Currently, not any specific drug is available for COVID-19 but still many countries under WHO leadership coordinating efforts to develop vaccine and medication to control this pandemic as early as possible.

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