

Review Article

SARS-CoV-2: Jumping the species barrier, lessons from SARS and MERS, its zoonotic spillover, transmission to humans, preventive and control measures and recent developments to counter this pandemic virus

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Abstract

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome - Coronavirus-2) of the family *Coronaviridae*, appeared in Wuhan, Hubei province, China being its epicenter in December 2019. This disease was declared as posing Public Health International Emergency by World Health Organization on January 30, 2020, attained the status of a very high-risk category on February 29, and now having a pandemic status (March 11, 2020). COVID-19 has presently spread to more than 195 countries/territories while killing nearly 19,600 humans out of cumulative confirmed cases accounting to more than 430,000 within a short period of just a few weeks. The majority of deaths have been reported in Italy and China. Researchers worldwide are pacing with high efforts to counter the spread of this virus and to design effective vaccines and therapeutics/drugs. Few of the studies have shown the potential of animal-human interface and zoonotic links in the origin of SARS-CoV-2. Exploring the possible zoonosis and revealing the factors responsible for its initial transmission from animals to humans will pave ways to design and implement effective preventive and control strategies to counter COVID-19. The present review presents an overview of COVID-19 and the causative virus SARS-CoV-2, with particular emphasis on the role of animals and their jumping the cross-species barriers, experiences learned from SARS- and MERS-CoVs, zoonotic links, and spillover events, transmission to humans and rapid spread., highlighting in very brief the preventive and control measures along with a few of the recent research developments to counter this pandemic virus/disease.

Keywords: COVID-19; SARS-Cov-2; bat coronavirus; zoonosis; spillover; expanding host range.

Running Title: Cross-species jumping of COVID-19 and recent research developments

1. Introduction

In the 21st century, we have faced a few deadly disease outbreaks caused by pathogenic viruses such as Bird flu caused by Avian influenza virus H5N1, Swine flu caused by reassorted influenza virus H1N1 pandemic 2009 (H1N1pdm2009), Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV (coronavirus), Middle East respiratory syndrome (MERS) caused by MERS-CoV, Ebola, Zika, Nipah virus infection, and the most recent threat, Coronavirus Disease - 2019 (COVID-19) that has been posed by Severe Acute Respiratory Syndrome - Coronavirus-2 (SARS-CoV-2 / novel coronavirus - 2019-nCoV) of the family *Coronaviridae*, genus *Betacoronavirus* (Dhama et al., 2012, 2018, 2020; Munjal et al., 2017; Singh et al., 2019; Malik et al., 2020; Stein et al., 2020). This virus emerged from the city of Wuhan, Hubei province, China during December 2019, was declared as Public Health International Emergency by the World Health Organization (WHO) on January 31, 2020. This was categorized in a high-risk category on February 29, 2020, and gained the pandemic status on March 11, 2020. The disease emerged from Wuhan, China as its epicentre, and subsequently, within a short time interval of 10 weeks, it has affected nearly 195 countries/territories and claimed 19,607 human deaths with confirmed cases of more than 435,000. The lessons learned from earlier threats of SARS, MERS and the present COVID-19 pandemic situations warrants designing and implementing some modified plans and strategies to combat emerging and zoonotic pathogens that could pose pandemic threats/risks while taking away many human lives (Azamfirei, 2020; Cohen and Kupferschmidt, 2020; Rodriguez-Morales et al., 2020a, 2020b; Khan et al., 2020; Malik et al., 2020; Peeri et al., 2020; Watts et al., 2020).

The most number of deaths from COVID-19 have been reported from Italy (6820), while deaths occurred in other countries include Spain (3434), China (3281), Iran (2077), France (1100), USA (784), UK (422), Netherlands (276), Belgium (178), Germany (172) and many other countries. Researchers and health agencies across the world are putting very high efforts to contain/restrain the spread of this deadly disease, and are pacing to develop potential vaccines and therapeutics/drugs. Evidence from the initial outbreak indicate earlier cases had links to Huanan Wholesale Seafood Market in China (Chen et al. 2020a) and further isolation of SARS-CoV-2 from different samples of the area (people, animals, birds, discharges, soil, structures) suggests the involvement of intermediate hosts (WHO 2020a). Recently, a literature of review has pointed out the possible potential role of the animal-human interface, zoonotic links and spillover events towards the origin of SARS-CoV-2/ COVID-19 (Ji et al., 2020a; Li et al., 2020a; Malik et al., 2020; Murdoch and French, 2020; Rodriguez-Morales et al., 2020a; Salata et al., 2020).

The SARS-CoV-2 is also thought to have originated from bats just like SARS-CoV and MERS-CoV. Civets and dromedary camels are considered as the intermediate host of SARS- and MERS-CoV, respectively, from where they were transmitted to humans (Park et al., 2020). The possible source of virus origin and the intermediate host of SARS-CoV-2 are yet to be identified. Initially, when the novel virus emerged in China, a hypothesis was put forward, claiming the recent recombination event as the cause of SARS-CoV-2 emergence. Nevertheless, the phylogenetic and recombination analysis performed within subgenus of *Sarbecovirus* demonstrated that the novel virus shows discordant clustering with Bat-SARS-

like coronavirus (RaTG13) sequences thus rejecting the possibility of a recent recombination event (Paraskevis et al., 2020). Previously, it was found that the continuous passaging of MERS-CoV in non-susceptible cells that express viral receptor led to the accumulation of mutations in the spike protein gene. This paid attention to the potential of coronaviruses like MERS-CoV to undergo mutations that enhance viral entry into novel animal species, thus resulting in cross-species transmission (Letko et al., 2018). The COVID-19 outbreak is still associated with several unanswered questions like the possibility of shedding of the virus before the onset of clinical signs, whether the transmission is limited to only through respiratory droplets, the possibility of an intermediate host that is responsible for zoonotic spillover, and the possible transmission characteristics (Lu et al., 2020a; Rodriguez-Morales et al., 2020a). In addition, this pandemic left the china with a massive blow on its economy which is not going to heal soon (Ayittey et al., 2020). In lieu of the current situation, Singapore's Prime Minister Lee Hsien Loong rightly said that the virus may have started in China but it doesn't respect nationality or race, doesn't check your passport before it goes into your body and anybody can be infected, hence all suspected people need to be tested and quarantined (Ren et al., 2020a).

Further researches, revealing the associated zoonosis and mechanisms accounting for its initial transmission from animals to humans, will lead to sort out the spread of this virus as well as design and develop appropriate prevention and control strategies to counter COVID-19. The present comprehensive manuscript presents an overview on COVID-19, an emerging SARS-CoV-2 infectious disease while focusing mainly on the events and circumstantial evidences with regards to this virus jumping the species barriers, sharing a few lessons learned from SARS- and MERS-CoVs, zoonotic spillover events (zoonosis), acquiring transmission ability to infect humans, and adopting appropriate preventive and control measures along with highlight some recent research developments which could aid to counter and restrain this emerging virus at the face of pandemic situations.

2. The Virus (SARS-CoV-2)

SARS-CoV-2 is an enveloped virus measuring approximately 50–200 nm in diameter with a single strand positive-sense RNA genome ranging from 26 to 32 kilobases in length (Lu et al. 2020b; Xu et al. 2020a). It has club-shaped glycoprotein spikes in the envelope, giving it a crown-like or coronal appearance (Chen et al. 2020a). The genome SARS-CoV-2 is comprised of 5' untranslated region (5' UTR) that includes 5' leader sequence, open reading frame (ORF) 1a/b (replicase genes), spike (S) protein, envelop (E) protein, membrane/matrix (M) protein, and accessory proteins (orf 3,6,7a, 7b, 8 and 9b), nucleoprotein (N), and 3' untranslated region (3' UTR) in their sequence (Han et al., 2020a). It has 50% genetic identity to MERS-CoV and 80% to SARS-CoV (Lu et al. 2020b; Ren et al. 2020b). The receptor-binding domain (RBD) of virus Spikes help in binding to cellular receptor angiotensin-converting enzyme 2 (ACE-2) (Wan et al. 2020; Wu et al. 2020). ORF and RBD of SARS-CoV-2 may have a role in elucidating cellular interactions and cross-species transmission mechanisms (Rothan and Byrareddy, 2020). Receptor binding motifs (RBM) have a role in interaction with human receptors, human to human transmission and cross-species transmission as Gln493 provides favourable interaction and Asn501 shows compatibility with human ACE-2 (Wan et al. 2020). In

addition, SARS-CoV-2 has superior transmission competence in comparison to the SARS-CoV leading to continuously increasing number of confirmed cases (Tian, 2020). SARS-CoV-2 has the potential to survive in the environment for several days (ECDC 2020). Though believed to be sensitive to environmental factors and alcohol-based sanitizers, bleach, and chloroform, the SARS-CoV-2 can survive in wet surroundings for days and in closed air conditions up to 12 hours (CDC 2020a; WHO 2020a). Survival of SARS-CoV-2 varies with respect to nature of surface, environment and virus load, and depending on the nature of surface like glass, fabric, metal, plastic or paper; can survive on surfaces for hours to several days such as can survive in aerosol for up to 3 hours and on plastic for up to 72 hours (WHO 2020a; van Doremalen et al. 2020).

3. The Disease (COVID-19)

The initial clinical picture of the COVID-19 was pneumonia of unknown origin as the early clinical cases were presented with signs of pneumonia (Lu et al. 2020a). Latter it was diagnosed as SARS-CoV-2 infection that was associated with severe pneumonia hence named as novel CoV pneumonia (NCP) (Xu et al., 2020b). As the outbreak proceeded, series of cases were produced developing a wide range of clinical signs with few remaining asymptomatic being in the early incubation stage of the disease. Thus COVID-19 is characterized by three major patterns of the clinical course of infection including mild illness producing upper respiratory signs, non-life threatening pneumonia and severe pneumonia with Acute Respiratory Distress Syndrome (ARDS) (Heymann et al. 2020). Initially, mild signs appear for 7-8 days, followed by rapid deterioration and ARDS. It can be mild to moderate in 80% of affected cases including pneumonia and non-pneumonia cases while as 13.8% are severe cases including dyspnea, respiratory distress, hemoptysis, gastro-intestinal infection, liver, central nervous system and lung damage cases (Guo et al., 2020; Xu et al., 2020c). Critical cases account for 6.1% and include respiratory failure, septic shock and multiple organ failure/dysfunction cases and few cases remain asymptomatic and include cases which can become any of the above during infection (WHO 2020a). Thus the symptoms can be non-specific and can range from no symptoms (asymptomatic) to severe pneumonia (WHO 2020a). In this context, a study concluded that the COVID-19 is probably overestimated, as around 2.6 million people succumb to respiratory diseases every year in comparison to around 15,000 deaths due to the SARS-CoV-2 infection (Roussel et al., 2020).

The typical clinical signs of COVID-19 are fever, chills, cough, fatigue, and chest distress (Bastola et al., 2020; Li et al., 2020b). Among these, fever and cough are considered as the most common symptoms in COVID-19 patients (Sun et al., 2020). Minor symptoms like headache, dyspnea, sore throat, hemoptysis, myalgia, diarrhoea, nausea, and vomiting are also observed (Li et al., 2020b; Sun et al., 2020). Some patients have shown rhinorrhea, confusion, chest pain, sputum production (Chen et al. 2020a), arthralgia, nasal congestion (WHO 2020a), anorexia, dizziness, pharyngalgia, and abdominal pain (Wang et al. 2020a). The characteristic of COVID-19 is attacking the lower respiratory tract and producing signs of upper respiratory distress, including rhinorrhea, sneezing, and sore throat (Rothan and Byrareddy, 2020). As reported, the clinical presentation of individuals infected with SARS-CoV-2 in Singapore, revealed upper respiratory tract infection, viraemia, viral shedding from nasopharynx and stool along with the development of nausea, vomiting or diarrhoea after

antiviral treatment (Young et al., 2020). On diagnostic imaging using computed tomography (CT scan) and radiography (X-ray) bilateral pneumonia, ground-glass opacity, multiple mottling, pneumothorax, infiltration, consolidation or bronchoinflation sign (bright bronchogram seen in the lung tissue area of the lesion) has been noted in many cases of COVID-19 (Chen et al. 2020a; Huang et al. 2020; Rothan and Byrareddy, 2020). The presence of neurological signs such as headache, vomiting, and nausea suggests that the pathogenesis is not limited/confined to the respiratory system. Previously, SARS-CoV was found to infect heavily the brainstem. The close similarity existing between SARS-CoV-2 and SARS-CoV indicates the possibility of neuro-invasive risk in COVID-19 also (Li et al., 2020c). Even though fever is considered as the most common symptom associated with COVID-19 infection, a large proportion of the patients do not express fever during the initial hospital admission (Guan et al., 2020). Respiratory distress is regarded as the most characteristic symptom of COVID-19 however clinical manifestations can vary as per immunity, age or gender.

The different transmission routes of SARS-CoV-2 infections have not yet been entirely ascertained, and are still under investigation. Both direct and indirect routes of transmission are being explored (Cai et al. 2020). Similar to SARS and MERS, SARS-CoV-2 is predominantly spread via the respiratory route (Chan et al. 2020). Person to person transmission is main reason for community and global spread. The initial estimated reproduction number (Ro-value) of COVID-19 was assessed to be from 0.8 to 2.4 in December 2019, which later has been increased to a mean value of 2.6 (range 2.1-5.1) (Lai et al., 2020a). Human-to-human transmission is by face-to-face contact with a sneeze or cough, or from contact with secretions of infected people (Chan et al. 2020; Heymann et al. 2020). Nevertheless, the infectivity of other secretions and excretions are not fully understood and may require further study (Han et al., 2020a). Aerosol and plastic surfaces can sustain virus for hours to days (van Doremalen et al. 2020). Travelling of infected people is considered as the main reason for the global spread of COVID-19 (Heymann et al. 2020; Rodríguez-Morales et al., 2020a). Although, the asymptomatic and mild cases are the major hurdle in evaluation of real number of infected people but the genuine data on travelers returning from affected countries or areas may prove crucial in estimating the disease incidence (Hoehl et al., 2020). The possible occurrence of super-spreading events is very high at large gatherings and suspension of gathering during pandemic may prove crucial in reducing the overall transmission (Liu et al., 2020a). Close contact with any person within 6 feet of the COVID-19 patient or anyone having direct contact with secretions of COVID-19 patients (Yee et al. 2020) may set up the infection. Unlike SARS-CoV most transmissions in COVID-19 are during the prodromal period when the infected individuals produce large quantities of virus in the upper respiratory tract, move/travel and usually work thus spreading virus before illness develops (Heymann et al. 2020). The rapid spread of COVID-19 among the susceptible population can be due to the wide variation in illness degrees that results in a missed diagnosis. Heavy viral load in asymptomatic cases and nosocomial transmission is spreading COVID-19 unknowingly (Wang et al. 2020b). Recently, high viral load was detected in the sputum of convalescent patient pointing out the possibility of prolonged shedding of SARS-CoV-2 even after recovery. This finding, along with the fact that asymptomatic persons can also act as the potential source of infection, may warrant a reassessment in the transmission dynamics of COVID-19 outbreak (Rothe et al., 2020). Presence of viral nucleic acids in

faeces is important finding, thereby increasing the possibility of faecal-oral transmission however symptoms may or may not be manifested (Gao et al., 2020). This was found to be the unique feature of COVID-19 and was lacking in the previous SARS and MERS outbreaks. In a study conducted by the Chinese CDC, it was found that the majority of patients (80.9%) infected with COVID-19 infection were either asymptomatic or had mild pneumonia. Such individuals are thought to release large amounts of viruses, mostly during the early phase of infection. Such prodromal asymptomatic cases travel or work normally before illness develops, and severely spread virus that can affect vulnerable persons (Heymann et al. 2020; Huang et al 2020).

Disease severity is found to be more in older individuals especially males with immunocompromised conditions and comorbidities like diabetes, asthma, or cardiovascular diseases (Huang et al. 2020; WHO 2020a). These are considered to be vulnerable to the SARS-CoV-2 infection. Predisposition increases under risk environment where transmission of virus from affected persons or contaminated fomites to unaffected ones becomes feasible. It was earlier noted that CoVs are not common to affect immunocompromised patients like other some viral infections (Influenza, Rhinovirus, Adenoviruses, to name a few). The current pandemic has shown SARS-CoV-2 to affect more lethally than young patients mainly destroying the lung tissues (D'Antiga 2020). Till now, evidence regarding the higher susceptibility of pregnant women in comparison to non-pregnant women lacks in COVID-19. Also, there is no evidence of vertical transmission (mother to fetus / baby transmission) of COVID-19 infection (Yang et al., 2020). A case study reporting the birth of a healthy infant by a SARS-CoV-2 infected woman suggests that mother-to-child transmission is unlikely in case of COVID-19. The study also pointed out that on the delivery day, all the samples tested negative except for sputum which tested positive (Li et al., 2020d). However, as per one most recent report, neonates have been found positive for SARS-CoV-2 indicating the possibility of vertical transmission from infected mothers to their progeny, thus rendering newborns into a high-risk group owing to their immature immune system (Wang et al., 2020c).

Individuals harboring SARS-CoV-2 may remain asymptomatic for the incubation period (Lauer et al. 2020). Different from SARS-CoV and MERS-CoV infection, the median incubation period of COVID-19 was found to be four days (Guan et al., 2020). The median period from development of signs to death was 14 days (Lei et al. 2020). The case fatality rate (CFR) of COVID-19 was found to be lower than MERS and SARS (Sun et al., 2020) however current disease dynamics with involvement of many more countries or areas, may change future mortality rate. The recent analysis suggests that the total fatality rate of COVID-19 is calculated at 3.46% (Wang et al., 2020b). However, Italy experienced the worst CFR of more than 9% with older people and male suffering from multiple comorbidities as main victims (Onder et al., 2020).

SARS-CoV-2 has shown characteristics of efficient replication in the upper respiratory tract, causing the less abrupt onset of clinical signs just like the common cold and unlike SARS-CoV (Chan et al. 2020). It can also replicate in the lower respiratory tract as has been noted in cases without pneumonia but having lesions in the lungs on radiological examination (Chan et al. 2020). The pathogenesis mechanisms of COVID-19 are yet to be fully elucidated. However both cellular and humoral immune responses against SARS-CoV-2 or its antigenic structures like spike protein (S) are believed to be of importance (Ahmed et

al. 2020; Tetro 2020) with disturbed levels of inflammatory mediators playing a mediating role (Huang et al. 2020). Following receptor binding with angiotensin converting enzyme 2 (ACE2) through receptor binding motif (RBM) of the receptor binding domain (RBD) of S1 subunit of the SARS-CoV-2 spike glycoprotein (S), virus gains entry in host cells (Hoffmann et al. 2020; Wan et al. 2020; Wrapp et al. 2020). S2 subunit helps in fusion of viral and host cell membranes (Coutard et al. 2020; Wan et al. 2020). Cytopathic effects are produced by SARS-CoV-2 in respiratory and gastrointestinal surface epithelial cells (Habibzadeh and Stoneman 2020). These include multinucleated syncytial cells, abnormally enlarged pulmonary cells, infiltration with mononuclear cells, lymphocytes infiltration in pulmonary organs, fibrinous exudation and hyaline deposition (Huang et al., 2020). Cytokine storm is believed to be involved in this inflammatory pathophysiology of the COVID-19 patients producing lung lesions and systemic symptoms (Huang et al. 2020). Elevated levels of TNF- α , IL1B, IFN γ , IP10, GCSF, MIP1A and MCP1, may have stimulated T-helper-1 (Th1) cells leading to this inflammatory cascade (Huang et al. 2020). However, levels of anti-inflammatory mediators (IL4, IL10) were also increased, indicating T-helper-2 (Th2) stimulation which suppresses inflammation, unlike what happens in SARS (Huang et al. 2020). A study documented that the nucleic acid of SARS-CoV-2 detected in the fecal samples was as accurate as that of pharyngeal samples obtained from infected patients. Moreover, the patients tested positive for SARS-CoV-2 in stool showed no gastrointestinal symptoms and had no relation to the severity of lung infections (Zhang et al., 2020a). One of the significant clinical signs of COVID-19 patients during the initial presentations were gastrointestinal symptoms. Hence involvement of GIT in pathogenesis needs to be explored. The significant laboratory findings include lymphopenia, increased values of erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, and decreased oxygenation index (Li et al., 2020b). Increase in proinflammatory cytokine and decrease in anti-inflammatory cytokines has also been noted (Huang et al. 2020). Viral isolation has been achieved from bronchio-alveolar lavage of affected persons however in case of pregnant women serum, feces, urine, breast milk, umbilical cord blood, placenta, and amniotic fluid were found to be negative for SARS-CoV-2 (Li et al., 2020d) while the sputum was tested positive (Wang et al., 2020c). Presence of abnormal coagulation parameters in patients with severe novel coronavirus pneumonia was associated with poor prognosis. The non-survivor patients had higher levels of D-dimer, and fibrin degradation product (FDP) along with longer activated partial thromboplastin time and prothrombin time compared to survivors at the time of admission (Tang et al., 2020a).

Though clinical manifestations, pathological changes and diagnostic laboratory findings can unravel the disease nature helping in devising therapeutic modalities however for epidemiological aspects and future prevention and control, simultaneous tracing of the origin and unraveling the spillover events can prove beneficial.

4. Virus jumping the species barrier, zoonotic spillover, transmission to humans

The SARS-CoV-2 has first been reported from the pneumonia patients of the Wuhan city in Hubei province of China. These patients were involved in trading at a wet animal market in Huanan area. It is believed that SARS-CoV-2 is introduced from the animal

kingdom to human populations during November or December 2019 as revealed from the phylogeny of the genomic sequences from the initially reported cases (GISAID 2020). The spillover of SARS-CoV-2 from animals to humans took place at the beginning of December 2019 (Heymann et al. 2020), and the clinical cases appeared around ending December (Du Toit 2020; Ren et al. 2020b). Genetic analysis showed that this novel virus is closely related to bat CoVs and is similar but distinct from the SARS virus (Lu et al. 2020b). Several evidences based on genome sequences, the homology of the ACE2 receptor and presence of single intact ORF on gene 8 indicate bats as a natural reservoir of these viruses, however an unknown animal is yet to be unravelled as intermediate host (Heymann et al. 2020; Lu et al. 2020b; Ren et al. 2020b; Rothan and Byrareddy 2020; Wan et al. 2020). Initial investigations on animal source origin of SARS-CoV-2 have inconclusively revealed snakes (Ji et al., 2020b), pangolins, and turtles (Liu et al., 2020b), and recently a Pomeranian dog (OIE, 2020a) as a probable intermediate host, however, such reports are yet to be validated, and research is underway to explore the emergence of this infectious disease at the animal-human interface (Murdoch and French, 2020; OIE 2020a). The initial animal to human spillover was followed by the rapid spread of COVID-19 through human-to-human transmission. Genetic epidemiology had also revealed that the spread from the beginning of December when the first cases were retrospectively traced in Wuhan was mainly by a human-to-human transmission and not due to continued spillover (Heymann et al. 2020). These species cross jumping, spillover and rapid transmission events are linked to viral characteristics, host diversity, and environmental feasibility.

Coronaviruses being RNA viruses have high mutation rates that besides creating new strains, enable them to adapt to a wide range of hosts, hence based on genome sequences all known human CoVs have emerged from animal sources (Cui et al. 2020). This seventh member of the human CoV has also been isolated initially from the pneumonia patients who were having direct or indirect links to Huanan seafood market in Wuhan China wherein other animals were also being sold (Zhu et al. 2020). These include a 49-year-old lady retailer in this wet animal market, a 61-year-old frequent visitor to this market and a 32-year-old man (Yee et al. 2020; Zhu et al. 2020). Further, isolation of the SARS-CoV-2 from the environmental samples around this market including people, animals, soil, discharges or structures strengthens the claims of involvement of hosts either as a reservoir or intermediate (CDC 2020a; OIE 2020a; WHO 2020a).

SARS-CoV-2 is the third zoonotic betacoronaviruses recognized in this century. Earlier identified betacoronaviruses were SARS-CoV, and MERS-CoV reported in Guangdong province of China in November 2002 and Saudi Arabia in 2012, respectively (Bonilla-Aldana et al., 2020a). However, the CFR of the COVID-19 is lower till date when compared with SARS and MERS, but it should not be overlooked as many asymptomatic cases may remain undiagnosed due to unavailability of diagnostic kits in China. With nearly 10,000 deaths till the preparation of the manuscript, SARS-CoV-2 is proven to be deadliest as far as the number of deaths is concerned in comparison with SARS-CoV and MERS-CoV with 774 and 858 associated deaths, respectively (Wang and Eaton, 2007; WHO, 2020b). Earlier, COVID-19 was linked with the exposure to Huanan seafood market, but individuals with no history of exposure above were also diagnosed with the illness, further supporting the human to human spread through droplets produced by cough and sneeze (Huang et al., 2020). However, the spread of COVID-19 that occurred with a high pace and lack of transparency in

reporting the disease by the Chinese Health Ministry and failure in the timely implementation of preventive measures has been considered as the primary contributor as reported earlier in SARS (Smith, 2006; Peeri et al., 2020). Both SARS-CoV and SARS-CoV-2 showed prominent similarity in their pathogenesis and epidemics. In both cases, bats were considered as the natural host and the cold temperature, and low humidity in cold, dry winter provided conducive environmental conditions that promoted the survival of the virus in the environment (Sun et al., 2020). Further, Moriyama et al. (2020), assessed the environmental factors significance on host immune system targeting innate and adaptive both responses in the respiratory tract.

The probability of the SARS-CoV-2 spread during incubation and convalescent period has been suggested (Rothe et al., 2020). As per reports, presence of coronaviruses has been observed in respiratory droplets, body fluids and inanimate objects with the ability to remain infectious for nine days on contaminated surfaces resulting in its risk of self-inoculation *via* mucous membranes of the eyes, mouth or nose (Dowell et al., 2004; Olofsson et al., 2005; Otter et al., 2016). Nosocomial, as well as human-to-human transmission, have been reported to occur *via* virus-laden aerosols, contaminated hands or surfaces and close community contact with an infected person (Huang et al., 2020; Kampf et al., 2020; Lee and Hsueh, 2020). The ocular route has been reported in the human-to-human transmission of SARS-CoV-2 as observed in SARS-CoV suggesting the involvement of different routes other than respiratory tract (Belser et al., 2013; Lu et al., 2020c). Later on, the probability of the faecal-oral route for potential transmission of the virus was also suggested (Holshue et al., 2020).

Since the beginning of 2002 till the end of 2019, three coronaviruses *viz.* SARS-CoV, MERS-CoV and SARS-CoV-2 have caused havoc in the human population globally and will continue to do so. A detailed investigation regarding the emergence of new coronavirus, host range and transmissibility is crucial to understand such pandemics shortly. The literature revealed that before the appearance of SARS-CoV and MERS-CoV, human coronavirus (HCoV) strains like HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1 were the CoVs strains producing mild infections in humans. However, their natural ancestral hosts were of animal origin, as bats for HCoV-NL63, and HCoV-229E and rodents were natural hosts for HCoV-OC43 and HKU1, and these four HCoVs were initially of low pathogenicity. To enhance the pathogenicity, they used intermediate hosts such as cattle for HCoV-OC43 (natural host was rodent), and alpacas for HCoV-229E (bats were natural host) and this way acquired the ability to infect human beings with serious health hazards (Lorusso et al., 2020).

It has been reported that almost all HCoVs have originated from animals like bats (SARS-CoV, MERS-CoV, HCoV-NL63 and HCoV-229E) and rodents (HCoV-OC43 and HKU1) (Su et al., 2016; Forni et al., 2017). Additionally, CoVs have been reported to infect several species of domestic and wild animals either clinically or subclinically (Ji et al., 2020a, 2020b; Li et al., 2020a, 2020e; Salata et al., 2020). Cattle, horses, camels, swine, dogs, cats, birds, rabbits, rodents, ferrets, mink, bats, snakes, frogs, marmots, hedgehogs, Malayan pangolin along with other wild animals may serve as a reservoir host of coronavirus (WHO 2003; Dhama et al., 2014a, 2014b; 2020; Monchatre-Leroy et al., 2017; Gravinatti et al., 2020; Ji et al., 2020a, 2020b; Lorusso et al., 2020; Xu, 2020; Xiao et al., 2020). In the context of SARS-CoV-2, snakes, pangolins and bats have been suspected as intermediate hosts since

the initial cases of COVID-19 had links to Huanan Sea Food Market where different animals, birds, and wild animals were being sold along with seafood items (Jalava 2020; Ji et al. 2020a, 2020b; Li et al. 2020a; Wang et al. 2020d; Lu et al. 2020b; Xiao et al., 2020). Among all the assumptions on animal hosts as the intermediate host, genomic and evolutionary information from pangolins reveal the highest closeness to the SARS-CoV-2 than any other hosts CoVs isolates (Zhang et al. 2020b). The spike protein, the main target of many studies finding a cure for COVID-19, has been found highly similar to SARS-CoV-2 and thus could serve as a surrogate system for further evaluations (Zhang et al. 2020b).

Bats are the natural reservoir host of many CoVs, including alphacoronaviruses and betacoronaviruses (Woo et al., 2012). As reported earlier, 7 out of 11 alphacoronaviruses and 4 out of 9 betacoronaviruses as per International Committee on Taxonomy of Viruses (ICTV) classification were solely originated from bats (Cui et al., 2019). According to the literature, bats have been regarded as a potential wildlife reservoir whereas civets and dromedary camels as intermediate hosts of SARS-CoV and MERS-CoV, respectively (Guan et al., 2003; Drosten et al., 2014). The bat coronavirus, BatCoV RaTG13, has shown higher relatedness to SARS-CoV-2 at complete genome level and spike gene in particular (Zhang et al. 2020b).

Coexistence and frequent recombination between highly diversified and prevalent bat SARS-related coronaviruses (SARSr-CoV) and coronaviruses may suggest the probable emergence of novel viruses in near future (Nagy and Simon, 1997; Rowe et al., 1997), Benvenuto et al. (2020) analyzed the whole genome sequences of different CoVs using Fast Unconstrained Bayesian AppRoximation (FUBAR) to understand the evolutionary and molecular epidemiology of SARS-CoV-2. The authors concluded that SARS-CoV-2 clustered with sequences of bat SARS-like CoVs with a few mutations in nucleocapsid and spike glycoprotein, suggesting its probable transmission from the bats (Benvenuto et al., 2020). As per the report, the metatranscriptome sequencing of SARS-CoV-2 in the bronchoalveolar lavage fluid (BALF) of infected individuals resulted in polymorphism in few intra-hosts variants, suggesting the *in vivo* evolution of the virus thereby affecting its virulence, transmissibility and infectivity (Shen et al., 2020a). Besides, based on Resampling Similarity Codon Usage (RSCU), snakes (*Bungarus multicinctus* and *Naja atra*) were suggested as wildlife reservoirs of SARS-CoV-2 and reported to be associated with the cross-species transmission (Ji et al., 2020a, 2020b) and later it was disapproved by other researchers (Callaway and Cyranoski, 2020; Robertson and Jiang, 2020). Unfortunately, till date, the intermediate host of the SARS-CoV-2 is abstruse what results in its escalation in human population around the globe. In this context, analyzing the interaction between the Asn501 site in RBD of spike glycoprotein of SARS-CoV-2 and the residue at 41 site of ACE2 receptor of different hosts (pangolins, turtle, mouse, dog, cat, hamster and bat) revealed that tyrosine has higher receptor binding affinity than histidine suggesting pangolins and turtle be more closer than bats to humans and may be the probable intermediate hosts of SARS-CoV-2 (Liu et al., 2020b). However, this hypothesis was also contradicted by Li et al. (2020a) based on an insertion of the unique peptide (PRRA) in SARS-CoV-2 virus, which was lacking in CoVs from pangolins.

Moreover, SARS-CoV-2 showed higher similarity to the BetaCoV/bat/Yunnan/RaTG13/2013 compared to the ones that were isolated from the pangolins, thereby denied the direct link of the virus from pangolins. However, further

studies are required to confirm the role of pangolins in SARS-CoV-2 spread to humans. As per the report, multiple substitutions were observed in ACE2 receptors of a dog (Liu et al., 2020b). In this context, a Pomeranian dog of the infected owner was tested positive for COVID-19, suggesting the permissiveness of the species for SARS-CoV-2 as a result of species jumping (OIE, 2020a; Promedmail, 2020).

The receptor-binding domain of the spike protein of SARS-CoV interacts with the host receptor ACE2 facilitating its potential of cross-species, as well as human-to-human transmission (Wan et al., 2020). Similarly, the spike protein of SARS-CoV-2 was reported to recognize ACE2 receptors expressed in fish, amphibians, reptiles, birds and mammals and has more robust binding capacity (affinity) in comparison to SARS-CoV (Wrapp et al., 2020). This suggests their involvement as probable natural and intermediate hosts (Chen et al., 2020b), which may further help in the selection of animal models for epidemic investigation and preventing its spread (Wan et al., 2020). Bat origin CoVs have been found to cross the species barrier what favoured their transmission *via* recombination/mutations in the RBD. The evidence of a virus outbreak that occurred in Chinese pig farms suggests its possible cross-species transmission (Lau et al., 2007; Zhou et al., 2018). Also, murine cells were found permissive for SARS-CoV after substitution of His353 with Lys353 in ACE2 receptor of a mouse which suggests the role of residue changes in the cross-species and human-to-human transmission (Li et al., 2005a). Mutation in residues at position 479 and 487 of receptor binding motif (RBM) of SARS-CoV was reported to play a role in civet-to-human and human-to-human transmission, respectively (Song et al., 2005; Li et al., 2008).

Moreover, the presence of threonine at position 487 was reported to enhance the binding affinity of RBM for ACE2 receptor of civet and humans (Li et al., 2005b). However, many SARS-related coronaviruses (SARSr-CoV) have been reported in bats and used ACE2 receptors for entry into a host cell which showed its potential to infect humans directly without any intermediate host (Ge et al., 2013). In addition to this, no direct transmission of SARSr-CoV is reported from bats to humans till date. However, seropositivity on a serological investigation of individuals without prior exposure to SARS-CoV residing near bat caves in China revealed likely infection of humans by bat SARSr-CoV and related viruses (Wang et al., 2018). Besides, the interspecies transmission potential of SARSr-CoVs is due to the ORF8 gene (Fan et al., 2019).

Zoonotic spillover is the transmission of pathogens to humans from vertebrate animals (Plowright et al., 2017). At present, these spillovers are of significant concern as in the past, many spillovers in the form of Nipah, Hendra, Ebola, SARS, MERS and ongoing COVID-19 involving many animal species like pigs, horses, monkeys, camels, civets, among others, were documented. Bovine CoVs have been reported to infect children and thus possess zoonotic potential (Zhang et al., 1994; Suzuki et al., 2020). Coronaviruses have also been reported to cause salivary, enteric and respiratory infections in laboratory animals (mice, rat, guinea pig, and rabbit) and urinary tract infection, respiratory illness and reproductive disorder in poultry (Dhama et al., 2014b). In bovine, canine, feline and swine CoVs infections have resulted in diarrhea, enteritis, respiratory illness, gastro-intestinal affections and nervous symptoms (Zhang et al., 1994; Erles and Brownlie, 2008; Licitra et al., 2014; Tekes and Thiel, 2016; Suzuki et al., 2020). Coronavirus, namely- SW1, has been reported in captive beluga whale using a panviral microarray method (Mihindukulasuriya et al., 2008).

Interestingly, bats play a crucial role in all above mentioned spillovers, indicating their importance in the emergence of new viruses. The reason behind the emergence and broad host range of CoVs in the past and present might be due to unstable RNA-dependent RNA polymerase (RdRp), lack of proof-reading ability, high frequency of mutations in the receptor-binding domain of spike gene and genetic recombination (Su et al., 2016; Chen, 2020; Patel and Jernigan, 2020). Bat CoVs have high diversity, and great potential of spillover in different animal species as reported earlier in civet cat and dromedary camel leading to well-known pandemics SARS and MERS respectively along with the recent spillover in pigs resulted in swine acute diarrhoea syndrome (SADS). However, spillover resulted in the emergence of SADS-CoV, which showed 95% genomic identity with bat coronavirus, led to severe mortality with 24,693 deaths in neonatal piglets (Zhou et al., 2018). Fortunately, it did not excel in the form of the third pandemic, and no human cases were reported till date. The spillover responsible for ongoing COVID-19 is still under investigation and a matter of great concern for the researchers all around the globe.

As per reports, the SARS-CoV emerged *via* recombination of bat SARSr-CoVs, was transmitted to farmed civets along with other mammals and these infected civets spread the virus to market civets. The virus was reported to undergo mutations in infected market civets before its spillover to humans. Similarly, the MERS-CoV circulated for 30 years in camels before the pandemic (Muller et al., 2014; Cui et al., 2019) supporting the hypothesis that after species jumping the exogenous viruses opted for adaptation to the environment and host before spillover to humans (Ellwanger and Chies, 2018). Moreover, the possible spillover of other circulating bat SARSr-CoVs to humans from mammalian hosts soon is highly anticipated.

The species-specific variations in the host receptors limit the interaction with CoV spike protein, and this is responsible for the development of the species barrier that prevents spillover infection. Recently, the MERS-CoV spike was found to possess the capacity for adapting to species variation in the host receptor, dipeptidyl peptidase 4 (DPP4) (Letko et al., 2018). The mechanism expressed by MERS-CoV in adapting to infect cells of new species might be present in the other coronaviruses. Snakes, civets, and pangolins are considered as the potential intermediate hosts of COVID-19, however further confirmation is required by tracking the origin of the virus. This is critical for preventing further exposure to this fatal virus (Amodio et al., 2020). Bats especially horseshoe bats (*Rhinolophus* spp.) are considered to be the known reservoirs of SARS-related CoVs. Since the bat origin, CoVs have always caused outbreaks in humans, studying the diversity and distribution of coronavirus populations in the bats will help to mitigate future outbreaks in humans and animals (Zhou et al., 2018).

An overview of coronaviruses jumping the cross-species barriers, zoonotic CoVs transmitted from bats to animals before spillover to humans, and possible prospects for further transmission to mammalian hosts is depicted in **Figure 1**.

5. Diagnosis

Following the classical way of diagnosis, Koch's postulates and initial identification of the cause of infection in China was based on deciphering the virus structure in electron microscope (Lu et al. 2020a). Subsequently, COVID-19 is being diagnosed by nucleic acid-based methods or antigen-antibody based serological methods (WHO 2020a). They involve detection of viral RNA by real-time reverse transcription-polymerase chain reaction (RT-PCR) or antibodies by lateral flow assays, ELISA, virus neutralization involving either single or combined IgM and IgG detection (WHO 2020a). Few of the kits have been approved for the detection of COVID-19 in China, including 6 RT-PCR kits, one isothermal amplification kit, one virus sequencing product, and two colloidal gold antibody detection kits (WHO 2020a). Several protocols based on real-time RT-PCR are available for confirming the suspected cases of COVID-19. RT-PCR kits that are widely used for detecting COVID-19 in China are developed by the Beijing Genomic Institute (Pang et al., 2020). As across the world, passengers are travelling from China to different countries including Japan through airlines, hence for their quick screening, two nested-RT-PCR and two real-time RT-PCR assays were developed in Japan and standardized as per the regional conditions. By using these assays, a few cases were found positive for SARS-CoV-2 in Japan (Shirato et al., 2020). As per evidence, the COVID-19 has been thought to spread during the first week of January 2020 in travellers flew from China to Thailand suggesting its early transmission in Thailand (Okada et al., 2020). Although the RT-PCR-based detection of viral nucleic acid is considered as the standard test for diagnosing COVID-19, it is associated with several limitations. One of which is the high occurrence of false-negative results (Li et al., 2020b). The individual exhibiting clinical signs of novel coronavirus pneumonia may not test positive in RNA detection test at every stage of the disease. Both the RNA positive and negative cases of NCP shared almost similar clinical symptoms, thus increasing the chance of misdiagnosis or missed diagnosis. The only difference observed in the RNA-positive cases is that they tend to have dyspnea (Li et al., 2020b). Till now, serological assays for COVID-19 are not developed, but in the coming future, it will be elaborated and commercialized (Pang et al., 2020). Recently, a lateral flow immunoassay was developed that can detect both IgM and IgG antibodies against SARS-CoV-2 virus simultaneously from the blood samples. This test will give the results within 15 minutes and was found to possess 88.66% sensitivity and 90.63% specificity during the clinical studies (Li et al., 2020f).

Diagnostic imaging techniques like CT scan and X-ray have also been used for the clinical diagnosis and patient evaluation (Song et al. 2020). Computed tomography (CT) is an ideal tool that can be used for identifying the pulmonary lesions associated with novel coronavirus pneumonia (NCP) (Guan et al., 2020; Xu et al., 2020b). The most common radiographic picture observed on CT images of COVID-19 infected patients is the ground-glass opacity (Guan et al., 2020). In the CT scan image of periphery of lung appearance, the bilateral ground-glass opacities are indicative of COVID-19 pneumonia and radiologist can help in predicting the severity of acute respiratory distress syndrome by rapidly recognizing any abnormality in the lungs in the infected or suspected individuals (Kim, 2020; Lai et al., 2020b). The early stages of NCP are characterized by scattered and irregular patches of ground-glass opacity. In severe or critical patients, multiple patches of ground-glass opacities are observed along with consolidations (Xu et al., 2020b). As per a report, the CT imaging findings of COVID-19 in asymptomatic patients revealed bilateral pleural effusions before the appearance of symptoms which lacked in previously detected COVID-19 cases and

regarded beneficial in potential recognition of the disease (Lin et al., 2020). Further, Chung et al. (2020) summarized the CT observations with some additional features as parenchymal ground-glass and absence of lung cavitation, distinctive pulmonary nodules, pleural effusions, and lymphadenopathy.

X-ray radiographs have shown a decrease in lung brightness, patchy shadows, ground-glass opacity and condensation (Chen et al. 2020a). Recently, the presence of viral shedding in tears and conjunctival secretions of SARS-CoV-2 infected patients has been evaluated. Among the individuals screened, only one sample that is obtained from a patient with conjunctivitis gave positive RT-PCR results (Xia et al., 2020). This is a critical finding due to the probable infective nature of tears and conjunctival secretions produced by NCP patients with conjunctivitis. Notably, in addition to progressive pulmonary lesions seen in COVID-19 patients, rhabdomyolysis affecting lower limb with painful condition and fatigue are visualized. The early observation of signs of rhabdomyolysis could prove lifesaving for affected patients (Jin and Tong, 2020).

Haematological (white blood counts, differential counts, platelet counts), biochemical (C-reactive protein, lactate dehydrogenase levels) and immunological (cytokines and chemokines) parameters have been evaluated as diagnostic biomarkers for COVID-19 cases (Chen et al. 2020a; Huang et al. 2020; Lei et al., 2020). Decrease in lymphocytes (lymphopenia) (Huang et al. 2020), increase in C-reactive protein (Chen et al. 2020a) and inflammatory cytokines and chemokines like TNF- α , IL-2, IL-10, MCP1, IP10, IF γ (Huang et al. 2020) were some of the initial findings in COVID-19 patients.

Other diagnostic tests suggested are recombinant protein techniques, virus neutralization, pseudo-particle VN tests (CDC 2020a; OIE 2020a). For confirmation next-generation sequencing (Shi et al. 2020), for exploring relationships with other coronaviruses phylogenetic analysis (Lu et al. 2020b), for rapid identification and characterization of novel coronavirus genomes Genome Detective Coronavirus Typing Tool has been developed (Cleemput et al. 2020).

Various multiplex assays facilitating multiple viral gene targets in a single tube proven highly beneficial for simultaneous detection of several viral pathogens (Zhang et al., 2020c). Recently for real-time monitoring of COVID-19 an interactive web-based dashboard has also been reported (Dong et al. 2020) For better diagnosis and timely detection of COVID-19, RNA assays, antibody and antigen assays and point-of-care detection should be the immediate goals, when the multiplex diagnostic platforms need to be intermediate goals, and for long term goals prognostic biomarkers must be evolved (WHO 2020a).

6. Vaccines and Therapies

Presently, neither there is an effective antiviral, nor any vaccine available for treating the COVID-19 and researchers are working around the clock in order to make the appropriate therapeutics and proven vaccines available, which must be the top priority of current situation (Lu et al., 2020d; Rodriguez-Morales et al., 2020b; Shanmugaraj et al., 2020a). Even though several therapeutic and vaccine options are available at our disposal, none of them is supported by the clinical evidence (Pang et al., 2020; Moderna. 2020; NIAID 2020). Under the prevailing outbreak situations oxygen therapy (Jin et al. 2020), plasma therapy (Jin et al.

2020), immunoglobulins (Kui et al. 2020), interferons (Jin et al. 2020) and corticosteroids (Zhou et al. 2020a) have been utilized in the treatment of COVID-19 patients with a few broad acting antibiotics (Jin et al. 2020) or antivirals also (Chen et al. 2020a). As of now, none is being a specific treatment hence requiring experimental evaluations. Following the COVID-19 outbreak, several clinical trials have been registered for evaluating antiviral drugs, vaccines, glucocorticoids, antimalarial drugs, and plasma therapy, while Traditional Chinese Medicine (TCM) accounted for a half of the studies (Zhang et al., 2020d). The human monoclonal antibody (HmAb) CR3022 that is specific to SARS-CoV was found to bind the RBD of SARS-CoV-2 as well, indicating the possibility of cross-protection. The other SARS-CoV specific mAb's like m396 and CR3014 that targets ACE2 binding site failed to bind the spike protein of 2019-nCoV indicating that the cross-protection provided by the mAb depends upon the similarity between the SARS-CoV and 2019-nCoV domains against which the mAb targets (Tian et al., 2020). Research data suggest that the ACE2 can serve as the binding site for SARS-CoV-2 (Letko et al. 2020). Hence, the angiotensin receptor 1 (AT1R) blockers like losartan can be considered for experimental treatment for SARS-CoV-2 infections (Gurwitz, 2020). It is hypothesized that the use of ACE2-blocking drugs might be harmful in COVID-19 patients and hence other classes of antihypertensive drug should be preferred if required (Esler and Esler, 2020). But this hypothesis should require further confirmation. Recently, based on the current available data it was proven that the ACE2 inhibitors and angiotensin II type 1 receptor blockers have potential therapeutic role in reducing the mortality among the patients with cardiovascular diseases. Hence, it was recommended to use these drugs in COVID-19 patients with heart failure, myocardial infarction, or hypertension (Kuster et al., 2020). Even though several expression systems are available for biopharmaceutical proteins production, production of the viral proteins in plants (plant expression platform) can accelerate vaccine production against COVID-19 that is cost-effective way of producing on large scale (Shanmugaraj et al., 2020a).

Spike glycoprotein (S) of SARS-CoV-2 helps in binding with the ACE2 receptors of host cells wherein subunit S1 helps in entry and subunit S2 helps in fusion (Walls et al. 2020; Wrapp et al. 2020). SARS-CoV-2 spike glycoprotein (S) contains furin-like cleavage which is absent in lineage b CoVs including SARS-CoV, involved in life cycle, cellular tropism, and pathogenicity, and have potential for developing furin inhibitors, or furin-like protease recognition pattern (Coutard et al. 2020). As the need for prophylactics and therapeutics is rising with increase in number of affected cases and global spread of COVID-19, the search for specific and effective drugs and/or vaccines has also started. Identifying SARS-CoV-2 specific antivirals or vaccine can help a lot and for this these sites, receptors or enzymes discussed above, can be utilized as the potential targets for drug or vaccine development (Habibzadeh and Stoneman 2020; Casadevall and Pirofski 2020).

High similarity (96%) was observed in the 3C-like protease (3CL^{pro}) of SARS-CoV-2 and SARS-CoV when their three-dimensional models were compared. Due to this near-identical substrate specificities along with the high sequence identities between SARS-CoV-2 and SARS-CoV, specific inhibitors that are already developed for SARS-CoV enzymes can be utilized for SARS-CoV-2 (Chen et al., 2020c). Non-specific antiviral therapy by oseltamivir, antibacterial therapy by moxifloxacin, ceftriaxone, azithromycin, and glucocorticoid therapy has been used in treating affected patients (Wang et al. 2020a). The broad-acting antiviral drug, remdesivir (GS-5734) was found to possess efficacy against

MERS-CoV infection in the *in vivo* rhesus macaque model. Treatment with remdesivir either before or after infecting the animal with MERS-CoV reduced the replication of virus, disease severity, and lung pathology (de Wit et al., 2020). Virtual screening performed on the 3CL^{pro} molecular model has identified several antiviral candidates against SARS-CoV-2. Among which the drug combinations of velpatasvir/sofosbuvir (Epclusa) and ledipasvir/sofosbuvir (Harvoni) might have potential therapeutic use due to their dual inhibitory actions that is directed against two of the viral enzymes (Chen et al., 2020c).

Remdesivir should also be considered as a potential candidate for the treatment of COVID-19 due to its promising antiviral efficacy against MERS-CoV. Remdesivir and chloroquine have effectively inhibited SARS-CoV-2 *in vitro* (Wang et al. 2020e). The aminoquinoline, hydroxychloroquine has an N-hydroxy-ethyl side chain instead of the N-diethyl group seen in the chloroquine and is considered to possess less toxic effects (Sahraei et al., 2020). The drug hydroxychloroquine was found to possess antiviral activity that is highly similar to that of chloroquine. It acts by suppressing the activation of T cells thereby attenuating the progression of cytokine storm in COVID-19. It has several advantages like easy availability; safe clinical profile and low production cost making this drug a suitable alternative for pregnant women (Zhou et al., 2020b). Hence, in situations where chloroquine is unavailable or scarce, hydroxychloroquine can be considered as a suitable alternative for the treatment of COVID-19 patients.

Due to the possible neuroinvasion potential of SARS-CoV-2, the early stages of COVID-19 might require antiviral therapy administered through airway inhalation route to block its entry into the central nervous system (Li et al., 2020c). One patient infected with COVID-19 infection showing symptoms of respiratory distress, fever and pneumonia upon computerized tomography (CT) scan of chest in South Korea was treated with lopinavir/ritonavir drug, and quantitative RT-PCR reported confirmed reduction in the titer of coronavirus in the patient after administration of a drug (Lim et al., 2020).

Development of vaccines against SARS-CoV-2 virus is a time-consuming process. Even though vaccines might be effective against COVID-19, those vaccines that are based on viral-encoded S peptides might not be effective against the coronavirus outbreaks that may arise shortly since the virus mutations could make them futile. Indeed, new influenza virus strains emerge every year, requiring new immunizations annually (Gurwitz, 2020). The virus-based vaccines that use entire virus particles in the inactivated or attenuated form should prove valuable for controlling COVID-19 outbreak. In addition to the viral particle vaccines, subunit vaccines using candidates such as S1 protein or RBD elements of SARS-CoV-2 might act as potential vaccine targets in our quest for preventing this pandemic (Shang et al., 2020).

The mAbs are widely used due to their very high therapeutic potential in the treatment of many diseases. The mAb-based therapeutic approaches can be used for COVID-19 after taking into consideration our in-depth and existing knowledge on available neutralizing mAbs against previous coronaviruses, *i.e.*, SARS-CoV and MERS-CoV (Shanmugaraj et al., 2020b). Nevertheless, possibility of adverse side effect, *e.g.*, antibody-dependent enhancement (ADE) of viral replication and antibody-dependent cell-mediated cytotoxicity (ADCC) that might occur through the mAb-treatment require evaluation (Khandia et al., 2018; Tetro, 2020). Among the different possible drugs that can be used for

the management of COVID-19 are four important compounds including lopinavir/ritonavir, chloroquine, ribavirin, and arbidol. The compounds that have promise *in vivo* activity such as remdesivir, favipiravir, and darunavir are currently under clinical trials (Liu et al., 2020c). The results from the existing studies suggest that the low dose, short duration corticosteroid therapy (methylprednisolone) is beneficial for the clinical management of COVID-19 critical patients. Those patients who are under corticosteroid therapy should be monitored for short- and long- term adverse drug reactions (Zhou et al., 2020a).

7. Prevention and Control

As the days are passing, almost every day reports are revealing a consistent increase in the number of affected people, as well as more number of deaths, in total **195** different countries/territories and therefore WHO is gradually updating the recommendations for the prevention of SARS-CoV-2 transmission globally. A recently updated list of Feb 29, 2020, suggested essential features to be adopted at wide-scale (Watts et al., 2020). Currently, due to the lack of effective therapeutic options, the control of COVID-19 should be based on early detection and quarantine of suspected individuals, and by providing supportive treatments for the infected patients (Han et al., 2020a). The recent trends suggest that the implementation of public health measures alone would not be sufficient to eliminate the threat caused by COVID-19. The concept of One Health has found application here in COVID-19 prevention and control involving experts from medical, veterinary, wildlife, public health, social science and other administrative setups who are directly or indirectly linked to the various aspects of this contagious foodborne respiratory zoonotic disease (Bonilla-Aldana et al., 2020b; Dhama et al., 2013a; Harypursat and Chen 2020; Heymann et al. 2020; OIE, 2020b; Rothan and Byrareddy, 2020). In this context, all the countries must concentrate on monitoring of high risk individuals working in animal related sectors, control of animal reservoirs, strict vigilance over illegal animal trades and development of huge animal and public health facilities to mitigate the probable pandemics in near future (Pike et al., 2010; Yu et al., 2014).

At this moment, several clinical trials are ongoing to evaluate the clinical efficacy of several therapeutic agents. Such drugs will only help to limit the morbidity and mortality associated with COVID-19 outbreak, while the vaccines and prophylactics will play a significant role in the prevention of further disease transmission (Park et al., 2020). Besides, Dey et al. (2020) reported that the analysis of exploratory visual data using the available epidemiological information on COVID-19 from several open datasets readily provide information regarding the numbers of confirmed, death and recovered cases. Therefore, it is essential to understand the risks and adopt appropriate interventions. As reported by Jung et al. (2020), the real-time monitoring of epidemiological data and comparing with those occurred previously can aid in determining the risk beforehand the virological identification of the pathogen involved. Studies using mathematical models suggest that highly effective contact tracing along with the isolation of infected individuals is sufficient enough to control COVID-19 outbreak within three months. It has to be noted that the success of this strategy in controlling the outbreak depends upon the characteristics of both pathogen and the response (Hellewell et al., 2020). The previous zoonotic coronavirus infection, SARS was controlled employing strict enforcement of quarantine, widespread surveillance, immediate isolation of infected patients, and enforcement of community quarantine. All these public health

strategies have helped to interrupt the possibility of human-to-human transmission. The differences in the virus and disease characteristics will be the ultimate factor that determines the success of the same public health measures in the eradication of COVID-19 (Wilder-Smith et al., 2020).

One of the crucial aspects of COVID-19 prevention and control is the implementation of WHO and CDC guidelines in healthcare and community settings. These guidance's are related to the detection of cases, isolation of persons under investigation (PUI), quarantine of affected and in-contact persons, management of confirmed cases, contact location, minimizing further spread and involve steps at the hospital level, administrative level, and locality level (CDC 2020a; WHO 2020a). Training and awareness among healthcare providers (HCP) about the COVID-19, especially its transmission dynamics, is essential to prevent the risk of spread. Different facets are being explored for prevention and control, including individual, cluster or community-based scenarios. Therefore, WHO and CDC have issued guidelines based on these situations. The general principle involves hand hygiene and respiratory hygiene for all classes (CDC 2020a; WHO 2020a). OIE recommends guidelines of the WHO and advises on applying food hygiene and environmental hygiene in addition to hand hygiene and respiratory hygiene (WHO 2020a; OIE, 2020a). As the SARS-CoV-2 is reported in contaminated surfaces individuals may be infected if they touch the eyes, nose or mouth after touching these contaminated surfaces (Han et al., 2020b). The essential points for prevention and control include frequent hand washing with either soap or sanitizer (alcohol-based, bleach/chlorine, peracetic acid, chloroform), sneezing/coughing under arm/elbow, not touching eyes, nose, or mouth with contaminated hands/surfaces, covering mouth and nose with masks or using tissues during sneezing or coughing, proper disposal of secretions, discharges or tissues, maintaining distance from infected persons (3-6 feet), disinfection of area, avoiding visit to infected areas, crowded places, live animal market, wet market or animal product market during outbreaks, avoiding direct contact with affected animals, animals living in the market (*e.g.* stray dogs, cats, rodents, birds, bats) or surfaces in contact with such animals, avoiding consumption of uncooked or raw animal products (meat, milk, eggs) or contaminated food, recognition of suspected probable case, tracing of transmitting contact, avoiding contact with potentially contaminated animal waste or fluids on the soil or structures of shops, and market facilities and isolation of infected cases can help in prevention and control of COVID-19 (Adhikari et al., 2020; CDC 2020a; OIE 2020a; WHO 2020a). In South Korea, early sustained transmission of COVID-19 was reported and implementation of social distancing measures were suggested highly effective in rapid control of the pandemic (Shim et al., 2020).

WHO has issued an advisory to follow to the countries, travellers, public and medical health workers in order to prevent from acquiring the COVID-19 infection. Most importantly, the epidemiological surveillance system should be strengthened to notify any outbreak of flu or pneumonia-like infection and must be reported to WHO within 48 hours of such incidence (Thompson, 2020). In this context, introduction of GIS as a tool for animal disease monitoring and surveillance is utmost necessary to provide momentum to recording, reporting, cluster analysis, outbreak situation assessment and planning of disease control strategies (Dhama et al., 2013b). The government must encourage awareness campaigns through social media and on their official websites to guide the citizens regarding what preventive measures should be followed (WHO, 2020c). Moreover, countries fall under

lower-income and middle-income group must be supported financially and technically for the development of testing facilities and therapeutics for COVID-19 (Bedford et al., 2020).

Recommendations suggested that infected persons, old age people and those who are suffering from any chronic disease should avoid travelling to affected regions and must follow sanitation, clean food and good hygienic practices to prevent the spread of the virus. People are advised not to touch their face, nose, eyes and mouth frequently and should wash their hands with clean water and soap or should use sanitizer containing more than 60 % alcohol. Healthy people should avoid being in contact with COVID-19 infected people and patients must use clean tissue papers or cloths to cover their face during coughing and sneezing, which must be discarded in any disinfectant. As clinician has to deal with patients, they must use the proper personal protective equipment (PPE). Infected persons should wear face masks to avoid virus transmission through sneezing or coughing *via* droplet to the environment, but masks are not advised to healthy individuals. Centers for Disease Control and Prevention (CDC) recommended that sick people should stay at home or in hospitals and should not go to crowded areas (CDC, 2020b).

As many patients are continuously admitted and kept in isolation wards under observations in hospitals, they are hot-spot for the bedside medical health workers and as per one report from such severe and critical patients more than 1700 clinicians have already acquired the infection through nosocomial transmission mode, and hence respiratory care committee of Chinese thoracic society has issued a few points of recommendations to prevent further transmission of coronavirus. They advised that the patient should be isolated and must wear masks while providing high flow nasal cannula (HFNC) oxygen therapy in pneumonia patients. Additionally, use of extracorporeal membrane oxygenation (ECMO) might be initiated to ensure proper care and safe transfer of critically ill individuals. Moreover, ECMO preparedness is crucial to prevent transmission and respiratory-related mortalities in COVID-19 pandemic (Ramanathan et al., 2020). Similarly, filters should be present at the outlet of ventilators and masks should not have any exhalation port preferably, and if at all exhalation port is given, it should be covered with additional filter. If COVID-19 infected patients get breathing difficulty during transportation, ventilators should be provided, and heat-moisture exchanger should be used in the place of heated humidified part between patient and ventilator. If there is a requirement of aerosol treatment or nebulizer, dry powder inhaler with spacer or mesh nebulizer with supplementary filter should be used (Respiratory care committee of the Chinese Thoracic Society, 2020). Another committee of experts proposed preventive measures in children against 2019 novel coronavirus infection to keep the young ones safe from the COVID-19 infection (Shen et al., 2020b).

Looking into the serious concern of rapidly spreading SARS-CoV-2 / COVID-19 pneumonia cases from China to other countries, Chinese Center for Disease Control and Prevention has issued a guideline for the protection of passenger health during transit at transport stations like an airport, railway station, bus stand, auto-stand, harbor while acquiring the transportation facilities of aviation, railway, subway, bus, taxi, ship (Chen et al., 2020d; Novel Coronavirus Pneumonia Emergency Response Key Places Protection and Disinfection Technology Team, Chinese Center for Disease Control and Prevention, 2020). Some health departments in China are organizing training programs to spread the awareness among clinicians, medical staff and non-medical persons regarding prevention of virus

contamination in hospital atmosphere from the patients (Tang et al., 2020b). Although, China has controlled the COVID-19 to a highly satisfactory level but China needs to be prepared for the possible rebound as people returning after a long holiday may re-introduce the disease (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020).

The containment of SARS-CoV-2 in its country of origin is difficult due to rapid globalization beyond borders (Wood, 2020). In fact, travellers played a crucial role in giving the wings to SARS-CoV-2 for worldwide transmission (Biscayart et al., 2020; Rodriguez-Morales et al., 2020c; Wilson and Chen, 2020). Passengers who are returning from the COVID-19-affected countries must be screened initially at entry-point and should be monitored for the next 14 days for appearance of any symptoms of cold, cough, fever. If symptoms occur, they should be quarantined, and treatment should be provided. Implementation of precautionary measures is most famous for those countries or personnel who are engaged in deporting persons from affected countries to their own. They have to prevent virus transmission among travellers themselves and in crew members of flight or cruise/ship. Many steps such as before boarding the flight all passengers should be tested at the entry point, an infected person should be carried with utmost precaution. During travel, the sick person should be provided with appropriate medication and health support, disinfectant measures to keep the flight/cruise infection-free and after arrival to the destined place again health screening must be taken (WHO, 2020c). The outbreak of SARS-CoV-2 on the Diamond Princess cruise ship suggested cruise ships as a crucial source of community spread hence a transparent cross-national managemental guidelines related with treatment, isolation, quarantine and evacuation must be developed to mitigate such pandemics in near future (MacIntyre, 2020). There is an urgent need of intensified surveillance, capacity building and resource allocation in probably ill-prepared countries with moderate risk for rapid detection of imported cases followed by mitigation of further transmission (Rodriguez-Morales et al., 2020b, 2020d). Any suspected case must be diagnosed quickly; if found positive must be quarantined. Recovered patient must be observed for no recurrence or relapse of the COVID-19 in order to avoid the repeated incidence of an epidemic at the same place (Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association, 2020).

A schematic illustration of COVID-19 clinical signs, modes of transmission, important diagnostic methods, and advances in vaccine development along with salient prevention and control strategies are presented in Figure 2.

8. Conclusion and Futuristic Vision

With the rising number and worldwide spread of COVID-19, the need for global efforts relies heavily on the investigations carried out at infection sites to trace different aspects of this novel coronavirus outbreak. One of the critical facets and the earliest investigation must involve tracing the root cause, origin and source of this emerging infectious disease. Shreds of evidence have revealed various cross-species jumping or spillover from animals to humans of these zoonotic coronaviruses. Detailed serological investigation of all domestic and wild animals residing in the proximity to humans is utmost

necessary to know and prevent likely spillover of many other bat-related CoVs in future. Rapid detection of spillovers above will only be possible by the implementation of an effective and robust surveillance system for circulating viruses with high zoonotic potential in animals. Besides, detection of a pathogen while crossing the species barrier to start circulation among humans and prevention of human-to-human transmission in early-stage may prove crucial in termination of a probable epidemic or pandemic. Application of 'One Health' concept involving medical, veterinary, wildlife, public health and other related professionals may help in infection tracing, exploring risk factors and predisposition, minimizing risk to susceptible ones, and finally devising better prevention and control strategies.

In the initial stages of COVID-19 outbreak, the steps taken for implementing stringent control and preventive measures have bought us some time. This time has to be efficiently utilized for developing SARS-CoV-specific therapeutic drugs and vaccines that can prevent the further spread of this fatal pathogen. For the time being early detection, isolation, and management of COVID-19 infected cases and for the immediate future awareness and implementation of the necessary steps of prevention and control to under risk and predisposed groups may help in long term prevention and control goals. However, it is clearly understood that relying exclusively on public health measures will not resolve the threat caused by COVID-19. Hence efforts to curb this emerging zoonosis at all levels need to be enforced under One Health approach.

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Figure Legends

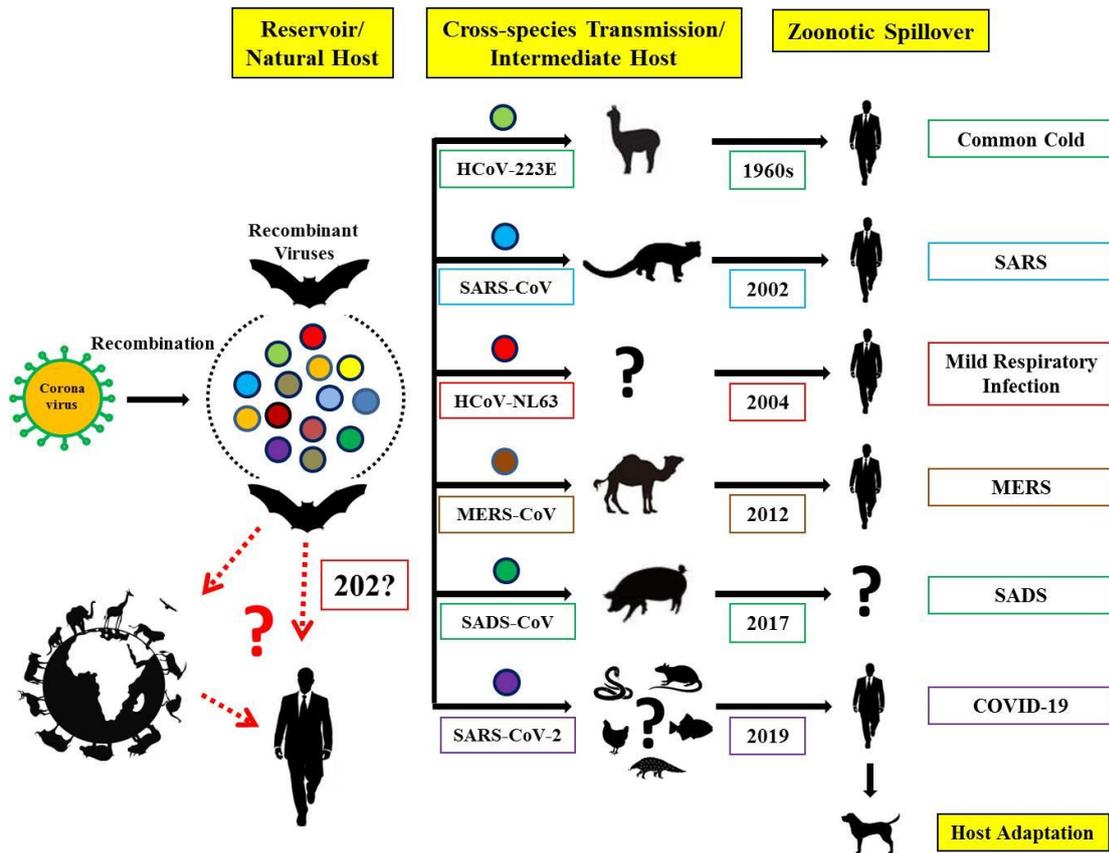


Figure 1: Cross-species transmission of known zoonotic coronaviruses from bats to animals before spillover to humans and probable prospects of further transmission to mammalian hosts.

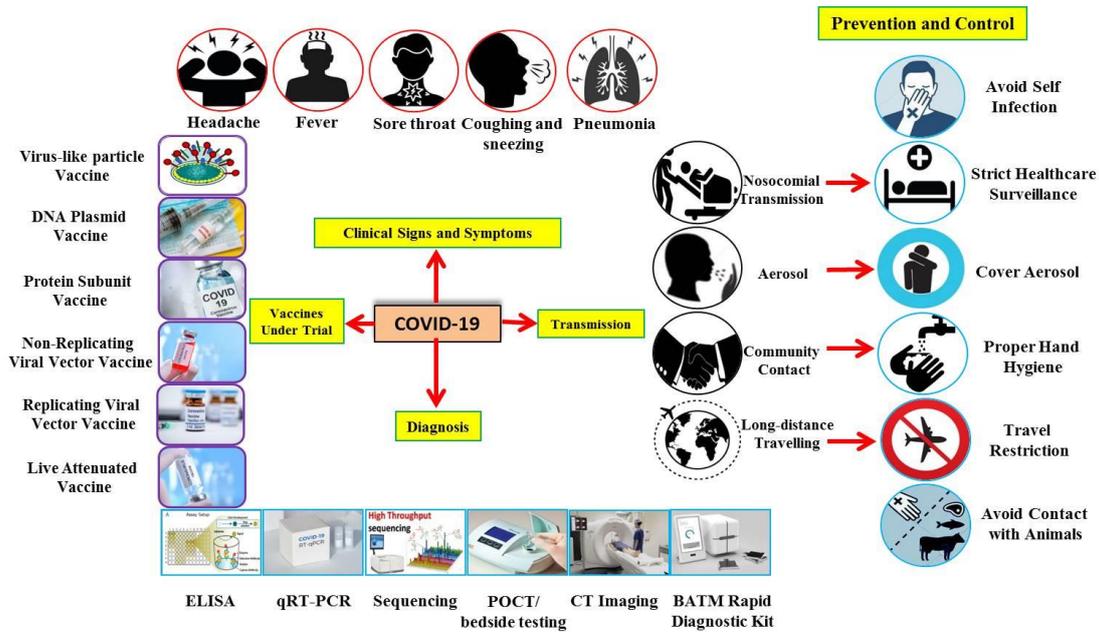


Figure 2: Schematic illustration of clinical signs, modes of transmission, advances in diagnosis and vaccine designing along with salient prevention and control strategies to counter COVID-19.