Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020

doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Kuldeep Dhama[1]*, Shailesh Kumar Patel[1], Khan Sharun[2], Mamta Pathak[1], Ruchi Tiwari[3], Mohd. Iqbal Yatoo[4], Yashpal Singh Malik[5], Ranjit Sah[6], Ali A. Rabaan[7], Parmod Kumar Panwar[8], Karam Pal Singh[1], Izabela Michalak[9], Wanpen Chaicumpa[10], D. Katterine Bonilla-Aldana[11,12], Alfonso J. Rodriguez -Morales.[12,13]*

[1]Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar 243 122, Bareilly, Uttar Pradesh, India.
[2]Division of Surgery, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India
[3]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, UP Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishwavidyalay Evum Go-Anusandhan Sansthan (DUVASU), Mathura, India –281001
[4]Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, 190025 Srinagar, Jammu and Kashmir, India
[5]Division of Biological Standardization, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India;
[6]Department of Microbiology, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal.
[7]Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
[8]Department of Animal Husbandry, Lucknow-2260007, Uttar Pradesh, India
[9]Faculty of Chemistry, Department of Advanced Material Technologies, Wrocław University of Science and Technology, Wrocław 50-370, Poland
[10]Center of Research Excellence on Therapeutic Proteins and Antibody Engineering, Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
[11]Semillero de Zoonosis, Grupo de Investigación BIOECOS, Fundación Universitaria Autónoma de las Américas, Sede Pereira, Pereira, Risaralda, Colombia;
[12]Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Colombia
[13]Grupo de Investigacion Biomedicina, Faculty of Medicine, Fundacion Universitaria Autonoma de las Americas, Pereira, Risaralda, Colombia

Corresponding Author(s):

Kuldeep Dhama, PhD (kdhama@rediffmail.com), Division of Pathology, ICAR –Indian Veterinary Research Institute, Izatnagar, Bareilly, India

Alfonso J Rodriguez-Morales, HonDSc (arodriguezm@utp.edu.co), Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Colombia.

© 2020 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

addition, SARS-CoV-2 has superior transmission competence in comparison to the SARS-CoV leadng 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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

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, IFNγ, 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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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, IFγ (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.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

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

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

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.

Acknowledgements

All the authors acknowledge and thank their respective Institutes and Universities.

Author contributions

All the authors substantially contributed to the conception, design, analysis and interpretation of data, checking and approving the final version of the manuscript, and agree to be accountable for its contents.

Funding

This compilation is a review article written, analyzed and designed by its authors and required no substantial funding to be stated.

Disclosure statement

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

References

1. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, Sun C, Sylvia S, Rozelle S, Raat H, Zhou H. 2020. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty. 9: 29. doi: 10.1186/s40249-020-00646-x.
2. Ahmed SF, Quadeer AA, McKay MR. Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies. Viruses. 2020;12(3):E254. doi: 10.3390/v12030254.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

3. Amodio E, Vitale F, Cimino L, Casuccio A, Tramuto F. Outbreak of Novel Coronavirus (SARS-Cov-2): First evidences from International Scientific Literature and Pending Questions. Healthcare 2020;8(1):51. https://doi.org/10.3390/healthcare8010051.
4. Ayittey FK, Ayittey MK, Chiwero NB, Kamasah JS, Dzuvor C. 2020. Economic Impacts of Wuhan 2019-nCoV on China and the World. Journal of Medical Virology. doi: 10.1002/jmv.25706.
5. Azamfirei R. The 2019 Novel Coronavirus: A Crown Jewel of Pandemics? J Crit Care Med (TarguMures). 2020. 6(1):3-4. doi: 10.2478/jccm-2020-0013.
6. Bastola A, Sah R, Rodriguez-Morales AJ, et al. The first 2019 novel coronavirus case in Nepal. Lancet Infect Dis 2020;20(3):279-80. doi:10.1016/S1473-3099(20)30067-0.
7. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, Lane HC, Memish Z, Oh MD, Sall AA, Schuchat A, Ungchusak K, Wieler LH; WHO Strategic and Technical Advisory Group for Infectious Hazards. COVID-19: towards controlling of a pandemic. Lancet. 2020:S0140-6736(20)30673-5. doi: 10.1016/S0140-6736(20)30673-5.
8. Belser JA, Rota PA, Tumpey TM. Ocular tropism of respiratory viruses. Microbiol Mol Biol Rev 2013;77(1):144-56. https://doi.org/10.1128/MMBR.00058-12.
9. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. J Med Virol 2020;92(4):455-459. https://doi.org/10.1002/jmv.25688.
10. Biscayart C, Angeleri P, Lloveras S, Chaves T, Schlagenhauf P, Rodriguez-Morales AJ. The next big threat to global health? 2019 novel coronavirus (2019-nCoV): What advice can we give to travellers? - Interim recommendations January 2020, from the Latin-American society for Travel Medicine (SLAMVI). *Travel Med Infect Dis.*, 2020: 101567. https://doi.org/10.1016/j.tmaid.2020.101567
11. Bonilla-Aldana DK, Quintero-Rada K, Montoya-Posada JP, Ramirez S, Paniz-Mondolfi A, Rabaan A, et al. SARS-CoV, MERS-CoV and now the 2019-novel CoV: Have we investigated enough about coronaviruses? - A bibliometric analysis. Travel Med Infect Dis. 2020a:101566.
12. Bonilla-Aldana DK, Dhama K, Rodriguez-Morales AJ. Revisiting the One Health Approach in the Context of COVID-19: A look into the Ecology of this Emerging Disease. Adv. Anim. Vet. Sci. 2020b. 8(3):234-237.
13. Cai J, Sun W, Huang J, Gamber M, Wu J, He G. Indirect virus transmission in cluster of COVID-19 cases, Wenzhou, China, 2020. Emerg Infect Dis. 2020 Jun [*date cited*]. https://doi.org/10.3201/eid2606.200412.
14. Casadevall A, Pirofski L. 2020. The convalescent sera option for containing COVID-19. J Clin Invest http://doi.org/10.1172/JCI138003.
15. CDC. 2020a. Coronavirus Disease 2019 (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/summary.html. Accessed on 1st March 2020.
16. CDC. 2020b. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Prevention & Treatment. https://www.cdc.gov/coronavirus/2019-ncov/about/prevention-treatment.html.
17. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. S0140-6736(20)30154-9. doi: 10.1016/S0140-6736(20)30154-9.
18. Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. Microbes Infect 2020;4:S1286-4579(20)30026-5. https://doi.org/10.1016/j.micinf.2020.01.004.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

19. Chen, N., M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet. 2020a. 395 (10223) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.
20. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. Biochem Biophys Res Commun. 2020b;S0006-291X(20)30339-9. https://doi.org/10.1016/j.bbrc.2020.02.071.
21. Chen YW, Yiu CB, Wong KY. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F1000Res. 2020c; 9:129. doi: 10.12688/f1000research.22457.1.
22. Chen W, Wang Q, Li YQ, Yu HL, Xia YY, Zhang ML, Qin Y, Zhang T, Peng ZB, Zhang RC, Yang XK, Yin WW, An ZJ, Wu D, Yin ZD, Li S, Chen QL, Feng LZ, Li ZJ, Feng ZJ. Early containment strategies and core measures for prevention and control of novel coronavirus pneumonia in China. Zhonghua Yu Fang Yi Xue Za Zhi, 2020d;54(3):1-6.
23. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-151. Chinese. doi: 10.3760/cma.j.issn.0254-6450.2020.02.003.
24. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020;200230. 10.1148/radiol.2020200230.
25. Cleemput S, Dumon W, Fonseca V, Karim WA, Giovanetti M, Alcantara LC, Deforche K, de Oliveira T. Genome Detective Coronavirus Typing Tool for rapid identification and characterization of novel coronavirus genomes. Bioinformatics. 2020 Feb 28:btaa145. doi: 10.1093/bioinformatics/btaa145.
26. Cohen J, Kupferschmidt K. Strategies shift as coronavirus pandemic looms. Science. 2020. 367(6481):962-963. doi: 10.1126/science.367.6481.962.
27. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. 2020. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 176:104742. doi:10.1016/j.antiviral.2020.104742.
28. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019;17(3):181-192. https://doi.org/10.1038/s41579-018-0118-9.
29. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA 2020;13:201922083. https://doi.org/10.1073/pnas.1922083117.
30. D'Antiga L, Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl. 2020 Mar 20. doi: 10.1002/lt.25756.
31. Dey SK, Rahman MM, Siddiqi UR, Howlader A. Analyzing the Epidemiological Outbreak of COVID-19: A Visual Exploratory Data Analysis (EDA) Approach. J Med Virol. 2020. https://doi.org/10.1002/jmv.25743.
32. Dhama K, Verma AK, Rajagunalan S, Deb R, Karthik K, Kapoor S, Mahima, Tiwari R, Panwar PK, Chakraborty S. Swine flu is back again: a review. Pak J Biol Sci 2012;15(21):1001-9. https://doi.org/10.3923/pjbs.2012.1001.1009.
33. Dhama K, Chakraborty S, SK, Tiwari R, Kumar ARD *et al.* One world, one health - Veterinary perspectives. Adv Anim Vet Sci. 2013a;1:5-13. https://doi.org/10.1155/2014/508304
34. Dhama, K., Verma, A.K., Tiwari, R., Chakraborty, S., Vora, K., Kapoor, S., Deb, R., Karthik, K., Singh, R., Munir, M. and Natesan, S. A perspective on applications of geographical information system (GIS); an advanced tracking tool for disease surveillance and monitoring in veterinary epidemiology. Adv Anim Vet Sci. 2013b;1(1):14-24.

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

35. Dhama K, Karthik K, Khandia R, Chakraborty S, Munjal A, Latheef SK, Kumar D, Ramakrishnan MA, Malik YS, Singh R, Malik SVS, Singh RK, Chaicumpa W. Advances in Designing and Developing Vaccines, Drugs, and Therapies to Counter Ebola Virus. Front Immunol 2018;9:1803. https://doi.org/10.3389/fimmu.2018.01803.
36. Dhama K, Pawaiya RVS, Chakraborty S, Tiwari R, Saminathan M, Verma AK. Coronavirus infection in equines: A review. Asian J Anim Vet Adv 2014a;9(3):164-176. https://doi.org/10.3923/ajava.2014.164.176.
37. Dhama K, Singh SD, Barathidasan R, Desingu PA, Chakraborty S, Tiwari R, Kumar MA. Emergence of Avian Infectious Bronchitis Virus and its variants need better diagnosis, prevention and control strategies: a global perspective. Pak J Biol Sci 2014b;17(6):751-67. https://doi.org/10.3923/pjbs.2014.751.767.
38. Dhama K, Sharun K, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, Chaicumpa W, Bonilla-Aldana DK, Rodriguez-Morales, AJ. Coronavirus disease 2019 – COVID-19. *Preprints* 2020;2020030001. https://doi.org/10.20944/preprints202003.0001.v1.
39. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020. S1473-3099(20)30120-1. doi:10.1016/S1473-3099(20)30120-1
40. Dowell SF, Simmerman JM, Erdman DD, Wu JS, Chaovavanich A, Javadi M, Yang JY, Anderson LJ, Tong S, Ho MS. Severe acute respiratory syndrome coronavirus on hospital surfaces. Clin Infect Dis 2004;39(5):652-7. https://doi.org/10.1086/422652.
41. Drosten C, Kellam P, Memish ZA. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med 2014;371(14):1359-60. https://doi.org/10.1056/NEJMc1409847.
42. Du Toit, A. Outbreak of a novel coronavirus, Nat. Rev. Microbiol. 18 (123) (2020), https://doi.org/10.1038/s41579-020-0332-0.
43. ECDC 2020. European Center for Disease Prevention and Control. Interim guidance for environmental clearing in non-healthcare facilities exposed to SARS-CoV-2, ECDC. Stockholm; 2020.
44. Ellwanger JH, Chies JAB. Zoonotic spillover and emerging viral diseases - time to intensify zoonoses surveillance in Brazil. Braz J Infect Dis 2018;22(1):76-78. https://doi.org/10.1016/j.bjid.2017.11.003.
45. Erles K, Brownlie J. Canine respiratory coronavirus: an emerging pathogen in the canine infectious respiratory disease complex. Vet Clin North Am Small Anim Pract 2008;38(4):815-25, viii. https://doi.org/10.1016/j.cvsm.2008.02.008.
46. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020 Mar 11. doi: 10.1097/HJH.0000000000002450.
47. Fan Y, Zhao K, Shi ZL, Zhou P. Bat Coronaviruses in China. Viruses 2019;11(3):210. https://doi.org/10.3390/v11030210.
48. Forni D, Cagliani R, Clerici M, Sironi M. Molecular Evolution of Human Coronavirus Genomes. Trends Microbiol 2017;25(1):35-48. https://doi.org/10.1016/j.tim.2016.09.001.
49. Gao QY, Chen YX, Fang JY. 2019 novel coronavirus infection and gastrointestinal tract. J Dig Dis 2020;10.1111/1751-2980.12851. https://doi.org/10.1111/1751-2980.12851.
50. Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, Zhang YJ, Luo CM, Tan B, Wang N, Zhu Y, Crameri G, Zhang SY, Wang LF, Daszak P, Shi ZL. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013;503(7477):535-8. https://doi.org/10.1038/nature12711.
51. GISAID 2020. Genomic epidemiology of BetaCoV 2019-2020. http://www.gisaid.org./epiflu-applications/next-betacov-app/
52. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. 2020. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res. 7: 11. doi: 10.1186/s40779-020-00240-0.

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

53. Gravinatti ML, Barbosa CM, Soares RM, Gregori F. Synanthropic rodents as virus reservoirs and transmitters. Rev Soc Bras Med Trop. 2020;53:e20190486. https://doi.org/10.1590/0037-8682-0486-2019.
54. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 10.1056/NEJMoa2002032. https://doi.org/10.1056/NEJMoa2002032.
55. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ, Butt KM, Wong KL, Chan KW, Lim W, Shortridge KF, Yuen KY, Peiris JS, Poon LL. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 2003;302(5643):276-8. https://doi.org/10.1126/science.1087139.
56. Gurwitz, D. 2020. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Development Research, n/a(n/a). doi:10.1002/ddr.21656
57. Habibzadeh P, Stoneman EK. The novel coronavirus: A bird's eye view. Int J Occup Environ Med 2020;11:65-71. doi: 10.15171/ijoem.2020.1921.
58. Han Q, Lin Q, Jin S, You L. Recent insights into 2019-nCoV: a brief but comprehensive review. J Infect 2020a; S0163-4453(20)30087-6. https://doi.org/10.1016/j.jinf.2020.02.010.
59. Han Q, Lin Q, Ni Z, You L. Uncertainties about the transmission routes of 2019 novel coronavirus. Influenza Other Respir Viruses. 2020b. doi: 10.1111/irv.12735.
60. Harypursat V, Chen YK. Six weeks into the 2019 coronavirus disease (COVID-19) outbreak- it is time to consider strategies to impede the emergence of new zoonotic infections. Chin Med J (Engl). 2020 :10.1097/CM9.0000000000000760. doi: 10.1097/CM9.0000000000000760.
61. Hellewell, J., Abbott, S., Gimma, A., Bosse, N. I., Jarvis, C. I., Russell, T. W., . . . Eggo, R. M. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. The Lancet Global Health. doi:10.1016/S2214-109X(20)30074-7
62. Heymann DL, Shindo N, On behalf of the WHO Scientific and Technical Advisory Group for Infectious Hazards, 2020. COVID-19: what is next for public health. Lancet 395(10224): 542-545.
63. Hoehl S, Berger A, Kortenbusch M, Cinatl J, Bojkova D, Rabenau H, Behrens P, Böddinghaus B, Götsch U, Naujoks F, Neumann P, Schork J, Tiarks-Jungk P, Walczok A, Eickmann M, Vehreschild MJGT, Kann G, Wolf T, Gottschalk R, Ciesek S. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. N Engl J Med. 2020. doi: 10.1056/NEJMc2001899.
64. Hoffmann M, Kleine-Weber H Kruger N, Muller M, Drosten C, Pohlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular proteases TMPRSS2 for entry into target cells. bioRxiv.10.1101/2020.01.31.929042.
65. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK; Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;10.1056/NEJMoa2001191. https://doi.org/10.1056/NEJMoa2001191.
66. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5.
67. Jalava K. First respiratory transmitted food borne outbreak? Int J Hyg Environ Health. 2020 Feb 20;226:113490. doi: 10.1016/j.ijheh.2020.113490.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

68. Jin M, Tong Q. Rhabdomyolysis as Potential Late Complication Associated with COVID-19. Emerg Infect Dis. 2020 Mar 20;26(7). doi: 10.3201/eid2607.200445.
69. Ji W, Wang W, Zhao X, Zai J, Li X. Cross-species transmission of the newly identified coronavirus 2019-nCoV. J Med Virol. 2020a; 92(4):433-440. doi: 10.1002/jmv.25682.
70. Ji, W., Wang, W., Zhao, X., Zai, J., & Li, X. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. J Med Virol 2020b. https://doi.org/10.1002/jmv.25682.
71. Jin Y.H., L. Cai, Z.S. Cheng, H. Cheng, T. Deng, Y.P. Fan, et al., A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version), Mil. Med. Res. 7, 4 (2020). https://doi.org/10.1186/s40779-020-0233-6.
72. Jung SM, Kinoshita R, Thompson RN, Linton NM, Yang Y, Akhmetzhanov AR, Nishiura H. Epidemiological Identification of A Novel Pathogen in Real Time: Analysis of the Atypical Pneumonia Outbreak in Wuhan, China, 2019-2020. J Clin Med 2020;9(3):E637. https://doi.org/10.3390/jcm9030637.
73. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020;S0195-6701(20)30046-3. https://doi.org/10.1016/j.jhin.2020.01.022.
74. Khan S, Siddique R, Ali A, Xue M, Nabi G. Novel coronavirus, poor quarantine, and the risk of pandemic. J Hosp Infect. 2020. S0195-6701(20)30048-7. doi: 10.1016/j.jhin.2020.02.002.
75. Khandia R, Munjal A, Dhama K, Karthik K, Tiwari R, Malik YS, Singh RK, Chaicumpa W. (2018). Modulation of Dengue/Zika Virus Pathogenicity by Antibody-Dependent Enhancement and Strategies to Protect Against Enhancement in Zika Virus Infection. Front Immunol. 9:597. doi: 10.3389/fimmu.2018.00597. eCollection 2018. Review.
76. Kim H. Outbreak of novel coronavirus (COVID-19): What is the role of radiologists? Eur Radiol. 2020 Feb 18:10.1007/s00330-020-06748-2. https://doi.org/10.1007/s00330-020-06748-2.
77. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, Widmer AF, Osswald S. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J. 2020 Mar 20:ehaa235. doi: 10.1093/eurheartj/ehaa235.
78. Lai A, Bergna A, Acciarri C, Galli M, Zehender G. Early phylogenetic estimate of the effective reproduction number of Sars-CoV-2. J Med Virol. 2020a: 10.1002/jmv.25723. https://doi.org/10.1002/jmv.25723.
79. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020b;55(3):105924. doi: 10.1016/j.ijantimicag.2020.105924.
80. Lau SK, Woo PC, Li KS, Huang Y, Wang M, Lam CS, Xu H, Guo R, Chan KH, Zheng BJ, Yuen KY. Complete genome sequence of bat coronavirus HKU2 from Chinese horseshoe bats revealed a much smaller spike gene with a different evolutionary lineage from the rest of the genome. Virology 2007;367(2):428-439. https://doi.org/10.1016/j.virol.2007.06.009.
81. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 Mar 10. doi: 10.7326/M20-0504. [Epub ahead of print].
82. Lee PI, Hsueh PR. Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV. J Microbiol Immunol Infect 2020;S1684-1182(20)30011-6. https://doi.org/10.1016/j.jmii.2020.02.001.
83. Lei, J. Li, J. Li, X. Qi X., CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia, Radiology (2020) 200236, https://doi.org/10.1148/radiol.2020200236.

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

84. Letko M, Miazgowicz K, McMinn R, Seifert SN, Sola I, Enjuanes L, Carmody A, van Doremalen N, Munster V. Adaptive evolution of MERS-CoV to species variation in DPP4. Cell Rep 2018;24(7):1730-1737. https://doi.org/10.1016/j.celrep.2018.07.045.
85. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for lineage B –coronavirus , including 2019-nCoV. Nat Microbiology 2020. 10.1038/s41564-020-0688-y.
86. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005a; 309(5742):1864-8. https://doi.org/10.1126/science.1116480.
87. Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, Wong SK, Huang IC, Xu K, Vasilieva N, Murakami A, He Y, Marasco WA, Guan Y, Choe H, Farzan M. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J. 2005b;24(8):1634-43. https://doi.org/10.1038/sj.emboj.7600640.
88. Li F. Structural analysis of major species barriers between humans and palm civets for severe acute respiratory syndrome coronavirus infections. J Virol. 2008;82(14):6984-91. https://doi.org/10.1128/JVI.00442-08.
89. Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley BT, Chaillon A. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. J Med Virol 2020a;10.1002/jmv.25731. https://doi.org/10.1002/jmv.25731.
90. Li YY, Wang WN, Lei Y, Zhang B, Yang J, Hu JW, Ren YL, Lu QF. Comparison of the clinical characteristics between RNA positive and negative patients clinically diagnosed with 2019 novel coronavirus pneumonia]. ZhonghuaJie He He Hu Xi ZaZhi 2020b;43(0):E023. Chinese. https://doi.org/10.3760/cma.j.cn112147-20200214-00095.
91. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. J Med Virol 2020c;10.1002/jmv.25728. https://doi.org/10.1002/jmv.25728.
92. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, Zhou J, Cai H, Fang Q, Yu F, Fan J, Xu K, Chen Y, Sheng J. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. Emerg Infect Dis. 2020d, 17;26(6). doi: 10.3201/eid2606.200287.
93. Li X, Song Y, Wong G, Cui J. Bat origin of a new human coronavirus: there and back again. Sci China Life Sci 2020e;10.1007/s11427-020-1645-7. https://doi.org/10.1007/s11427-020-1645-7.
94. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, Sun R, Wang Y, Hu B, Chen W, Zhang Y, Wang J, Huang B, Lin Y, Yang J, Cai W, Wang X, Cheng J, Chen Z, Sun K, Pan W, Zhan Z, Chen L Ye F. Development and Clinical Application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol 2020f. https://doi.org/10.1002/jmv.25727.
95. Licitra BN, Duhamel GE, Whittaker GR. Canine enteric coronaviruses: emerging viral pathogens with distinct recombinant spike proteins. Viruses 2014;6(8):3363-76. https://doi.org/10.3390/v6083363.
96. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B, Park SJ. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of Lopinavir/Ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci 2020;35(6):e79. https://doi.org/10.3346/jkms.2020.35.e79.
97. Lin C, Ding Y, Xie B, Sun Z, Li X, Chen Z, Niu M. Asymptomatic novel coronavirus pneumonia patient outside Wuhan: The value of CT images in the course of the disease. Clin Imaging 2020;63:7-9. https://doi.org/10.1016/j.clinimag.2020.02.008.
98. Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. Lancet. 2020a, 27:S0140-6736(20)30462-1. doi: 10.1016/S0140-6736(20)30462-1.
99. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, Zhu J, Zhang Q, Wu J, Liu L. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol 2020b;10.1002/jmv.25726. https://doi.org/10.1002/jmv.25726

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

100. Liu W, Zhu HL, Duan Y. Effective Chemicals against Novel Coronavirus (COVID-19) in China. Curr Top Med Chem. 2020c. doi: 10.2174/1568026620999200305145032.
101. Lorusso A, Calistri P, Petrini A, Savini G, Decaro N. Novel coronavirus (SARS-CoV-2) epidemic: a veterinary perspective. Vet Ital. 2020 10.12834/VetIt.2173.11599.1. https://doi.org/10.12834/VetIt.2173.11599.1.
102. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol. 2020a;92(4):401–402. doi: 10.1002/jmv.25678.
103. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020b;395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8.
104. Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet 2020c;395(10224):e39. https://doi.org/10.1016/S0140-6736(20)30313-5.
105. Lu H, Stratton CW, Tang YW. The Wuhan SARS-CoV-2-What's next for China. J Med Virol. 2020d. doi: 10.1002/jmv.25738.
106. MacIntyre CR. On a knife's edge of a COVID-19 pandemic: is containment still possible? Public Health Res Pract. 2020;30(1):3012000. doi: 10.17061/phrp3012000.
107. Malik YS, Sircar S, Bhat S, Sharun K, Dhama K, Dadar M, Tiwari R, Chaicumpa W. Emerging novel coronavirus (2019-nCoV)-current scenario, evolutionary perspective based on genome analysis and recent developments. Vet Q 2020;40(1):68-76.. https://doi.org/10.1080/01652176.2020.1727993.
108. Mihindukulasuriya KA, Wu G, St Leger J, Nordhausen RW, Wang D. Identification of a novel coronavirus from a beluga whale by using a panviral microarray. J Virol 2008;82(10):5084-8. https://doi.org/10.1128/JVI.02722-07.
109. Moderna. 2020. Moderna Announces Funding Award from CEPI to Accelerate Development of Messenger RNA (mRNA) Vaccine Against Novel Coronavirus. https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-funding-award-cepi-accelerate-development (Accessed on February 15, 2020).
110. Monchatre-Leroy E, Boué F, Boucher JM, Renault C, Moutou F, Ar Gouilh M, Umhang G. Identification of Alpha and Beta Coronavirus in Wildlife Species in France: Bats, Rodents, Rabbits, and Hedgehogs. Viruses 2017;9(12):364. https://doi.org/10.3390/v9120364.
111. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of Respiratory Viral Infections. Annu Rev Virol. 2020 Mar 20. doi: 10.1146/annurev-virology-012420-022445.
112. Müller MA, Corman VM, Jores J, Meyer B, Younan M, Liljander A, Bosch BJ, Lattwein E, Hilali M, Musa BE, Bornstein S, Drosten C. MERS coronavirus neutralizing antibodies in camels, Eastern Africa, 1983-1997. Emerg Infect Dis 2014;20(12):2093-5. https://doi.org/10.3201/eid2012.141026.
113. Munjal A, Khandia R, Dhama K, Sachan S, Karthik K, Tiwari R, Malik YS, Kumar D, Singh RK, Iqbal HMN, Joshi SK. Advances in Developing Therapies to Combat Zika Virus: Current Knowledge and Future Perspectives. Front Microbiol 2017;8:1469. https://doi.org/10.3389/fmicb.2017.01469.
114. Murdoch DR and French NP. 2020. COVID-19: another infectious disease emerging at animal-human interface. New Zealand Medical Journal 133(1510):
115. Nagy PD, Simon AE. New insights into the mechanisms of RNA recombination. Virology 1997;235(1):1-9. https://doi.org/10.1006/viro.1997.8681.
116. NIAID 2020. Developing Therapeutics and Vaccines for Coronaviruses. https://www.niaid.nih.gov/diseases-conditions/coronaviruses-therapeutics-vaccines (Accessed on February 15, 2020).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

117. Novel Coronavirus Pneumonia Emergency Response Key Places Protection and Disinfection Technology Team, Chinese Center for Disease Control and Prevention. Health protection guideline of passenger transport stations and transportation facilities during novel coronavirus pneumonia (NCP) outbreak. Zhonghua Yu Fang Yi Xue Za Zhi 2020;54(0):E007. https://doi.org/10.3760/cma.j.cn112150-20200217-00130.

118. OIE. 2020a. Animal and environmental investigation to identify the zoonotic source of the COVID-19 virus. COVID19_21Feb.pdf. Accessed 04-03-2020.

119. OIE. 2020b. One Health. https://www.oie.int/en/for-the-media/onehealth/.

120. Okada P, Buathong R, Phuygun S, Thanadachakul T, Parnmen S, Wongboot W, Waicharoen S, Wacharapluesadee S, Uttayamakul S, Vachiraphan A, Chittaganpitch M, Mekha N, Janejai N, Iamsirithaworn S, Lee RT, Maurer-Stroh S. Early transmission patterns of coronavirus disease 2019 (COVID-19) in travellers from Wuhan to Thailand, January 2020. Euro Surveill 2020;25(8). https://doi.org/10.2807/1560-7917.ES.2020.25.8.2000097.

121. Olofsson S, Kumlin U, Dimock K, Arnberg N. Avian influenza and sialic acid receptors: more than meets the eye? Lancet Infect Dis 2005;5(3):184-8. https://doi.org/10.1016/S1473-3099(05)01311-3.

122. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020. doi: 10.1001/jama.2020.4683.

123. Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. J Hosp Infect 2016;92(3):235-50. https://doi.org/10.1016/j.jhin.2015.08.027.

124. Pang J, Wang MX, Ang IYH, Tan SHX, Lewis RF, Chen JI, Gutierrez RA, Gwee SXW, Chua PEY, Yang Q, Ng XY, Yap RK, Tan HY, Teo YY, Tan CC, Cook AR, Yap JC, Hsu LY. Potential rapid diagnostics, vaccine and therapeutics for 2019 novel Coronavirus (2019-nCoV): A systematic review. J Clin Med 2020;9(3):E623. https://doi.org/10.3390/jcm9030623.

125. Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel coronavirus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol 2020;79:104212.. https://doi.org/10.1016/j.meegid.2020.104212.

126. Park M, Thwaites RS, Openshaw PJM. COVID-19: Lessons from SARS and MERS. Eur J Immunol 2020; 10.1002/eji.202070035. https://doi.org/10.1002/eji.202070035.

127. Patel A, Jernigan DB; 2019-nCoV CDC Response Team. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak - United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep 2020;69(5):140-146. https://doi.org/10.15585/mmwr.mm6905e1.

128. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, Baghbanzadeh M, Aghamohammadi N, Zhang W, Haque U. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol 2020;dyaa033. https://doi.org/10.1093/ije/dyaa033.

129. Pike BL, Saylors KE, Fair JN, Lebreton M, Tamoufe U, Djoko CF, Rimoin AW, Wolfe ND. The origin and prevention of pandemics. Clin Infect Dis. 2010;50(12):1636-40. doi: 10.1086/652860.

130. Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, Lloyd-Smith JO. Pathways to zoonotic spillover. Nat Rev Microbiol 2017;15(8):502-510. https://doi.org/10.1038/nrmicro.2017.45.

131. Promed International society for infectious diseases (https://promedmail.org/promed post/?id=7036661).

132. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K. Planning and provision of ECMO services for severe ARDS during the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med. 2020:S2213-2600(20)30121-1. doi: 10.1016/S2213-2600(20)30121-1.

133. Ren SY, Gao RD, Chen YL. Fear can be more harmful than the severe acute respiratory syndrome coronavirus 2 in controlling the corona virus disease 2019 epidemic. World J Clin Cases. 2020a. 8(4): 652–657. doi: 10.12998/wjcc.v8.i4.652.

134. Ren L.L., Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, et al., Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chinese Med J 2020b. https://doi.org/10.1097/CM9.0000000000000722.

135. Respiratory care committee of Chinese Thoracic Society. Expert consensus on preventing nosocomial transmission during respiratory care for critically ill patients infected by 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;17(0):E020. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0020.

136. Rodriguez-Morales AJ, Bonilla-Aldana DK, Balbin-Ramon GJ, Rabaan AA, Sah R, Paniz-Mondolfi A, Pagliano P, Esposito S. History is repeating itself: Probable zoonotic spillover as the cause of the 2019 novel Coronavirus Epidemic. Infez Med. 2020a;28(1):3-5.

137. Rodriguez-Morales AJ, D. Katterine Bonilla-Aldana, Ruchi Tiwari, Ranjit Sah, Ali A. Rabaan, Kuldeep Dhama. COVID-19, an Emerging Coronavirus Infection: Current Scenario and Recent Developments – An Overview, J. Pure Appl. Microbiol., 2020b;14(1):6150.

138. Rodríguez-Morales AJ, MacGregor K, Kanagarajah S, Patel D, Schlagenhauf P. Going global - Travel and the 2019 novel coronavirus. Travel Med Infect Dis. 2020c;33:101578. doi: 10.1016/j.tmaid.2020.101578.

139. Rodríguez-Morales AJ, Gallego V, Escalera-Antezana JP, Mendez CA, Zambrano LI, Franco-Paredes C, Suárez JA, Rodriguez-Enciso HD, Balbin-Ramon GJ, Savio-Larriera E, Risquez A, Cimerman S. COVID-19 in Latin America: the implications of the first confirmed case in Brazil. Travel Med Infect Dis. 2020d. doi: 10.1016/j.tmaid.2020.101613.

140. Rothan HA, and Byrareddy SN, 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity. *In Press*. https://doi.org/10.1016/j.jaut.2020.102433.

141. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirglmaier K, Zange S, Wölfel R, Hoelscher M. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med. 2020 Mar 5;382(10):970-971. doi: 10.1056/NEJMc2001468.

142. Roussel Y, Giraud-Gatineau A, Jimeno MT, Rolain JM, Zandotti C, Colson P, Raoult D. SARS-CoV-2: fear versus data. Int J Antimicrob Agents. 2020:105947. doi: 10.1016/j.ijantimicag.2020.105947.

143. Rowe CL, Fleming JO, Nathan MJ, Sgro JY, Palmenberg AC, Baker SC. Generation of coronavirus spike deletion variants by high-frequency recombination at regions of predicted RNA secondary structure. J Virol. 1997’ 71(8):6183-90.

144. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines Against Coronavirus Disease 2019 (COVID-19): Chloroquine or Hydroxychloroquine. Int J Antimicrob Agents. 2020 Mar 16:105945. doi: 10.1016/j.ijantimicag.2020.105945.

145. Salata C, Calistri A, Parolin C, Palù G. Coronaviruses: a paradigm of new emerging zoonotic diseases. Pathog Dis. 2020 Dec 1;77(9):ftaa006. https://doi.org/10.1038/nm1143.

146. Shang W, Yang Y, Rao Y, Rao X. The outbreak of SARS-CoV-2 pneumonia calls for viral vaccines. NPJ Vaccines. 2020 Mar 6;5:18. doi: 10.1038/s41541-020-0170-0.

147. Shanmugaraj B, Malla A, Phoolcharoen W. Emergence of Novel Coronavirus 2019-nCoV: Need for rapid vaccine and biologics development. Pathogens 2020a;9(2):E148. https://doi.org/10.3390/pathogens9020148.

148. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). Asian Pac J Allergy Immunol. 2020b. doi: 10.12932/AP-200220-0773.
149. Shen Z, Xiao Y, Kang L, Ma W, Shi L, Zhang L, Zhou Z, Yang J, Zhong J, Yang D, Guo L, Zhang G, Li H, Xu Y, Chen M, Gao Z, Wang J, Ren L, Li M. Genomic diversity of SARS-CoV-2 in Coronavirus Disease 2019 patients. Clin Infect Dis 2020a;ciaa203. https://doi.org/10.1093/cid/ciaa203.
150. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, Zheng Y, Xu B, Xie Z, Lin L, Shang Y, Lu X, Shu S, Bai Y, Deng J, Lu M, Ye L, Wang X, Wang Y, Gao L; China National Clinical Research Center for Respiratory Diseases; National Center for Children’s Health, Beijing, China; Group of Respirology, Chinese Pediatric Society, Chinese Medical Association; Chinese Medical Doctor Association Committee on Respirology Pediatrics; China Medicine Education Association Committee on Pediatrics; Chinese Research Hospital Association Committee on Pediatrics; Chinese Non-government Medical Institutions Association Committee on Pediatrics; China Association of Traditional Chinese Medicine, Committee on Children’s Health and Medicine Research; China News of Drug Information Association, Committee on Children’s Safety Medication; Global Pediatric Pulmonology Alliance. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020b;10.1007/s12519-020-00343-7. https://doi.org/10.1007/s12519-020-00343-7.
151. Shi ZPZ, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, Hui-Dong Chen, Jing Chen, Yun Luo, Hua Guo, Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Xu- Rui Shen, Xi Wang, Xiao-Shuang Zheng, Kai Zhao, Quan-Jiao Chen, Fei Deng, Lin-Lin Liu, Bing Yan, Fa-Xian Zhan, Yan-Yi Wang, Gengfu Xiao. 2020. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. wwwbiorxiv.org.
152. Shim E, Tariq A, Choi W, Lee Y, Chowell G. Transmission potential and severity of COVID-19 in South Korea. Int J Infect Dis. 2020:S1201-9712(20)30150-8. doi: 10.1016/j.ijid.2020.03.031.
153. Shirato K, Nao N, Katano H, Takayama I, Saito S, Kato F, Katoh H, Sakata M, Nakatsu Y, Mori Y, Kageyama T, Matsuyama S, Takeda M. Development of Genetic Diagnostic Methods for Novel Coronavirus 2019 (nCoV-2019) in Japan. Jpn J Infect Dis. 2020; 10.7883/yoken.JJID.2020.061. https://doi.org/10.7883/yoken.JJID.2020.061.
154. Sun Z, Thilakavathy K, Kumar SS, He G, Liu SV. Potential Factors Influencing Repeated SARS Outbreaks in China. Int J Environ Res Public Health. 2020 Mar 3;17(5):E1633. doi: 10.3390/ijerph17051633.
155. Singh RK, Dhama K, Chakraborty S, Tiwari R, Natesan S, Khandia R, Munjal A, Vora KS, Latheef SK, Karthik K, Singh Malik Y, Singh R, Chaicumpa W, Mourya DT. Nipah virus: epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control strategies - a comprehensive review. Vet Q 2019;39(1):26-55. https://doi.org/10.1080/01652176.2019.1580827.
156. Smith RD. Responding to global infectious disease outbreaks: lessons from SARS on the role of risk perception, communication and management. Soc Sci Med 2006;63(12):3113-23. https://doi.org/10.1016/j.socscimed.2006.08.004.
157. Song HD, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, Chen QX, Gao YW, Zhou HQ, Xiang H, Zheng HJ, Chern SW, Cheng F, Pan CM, Xuan H, Chen SJ, Luo HM, Zhou DH, Liu YF, He JF, Qin PZ, Li LH, Ren YQ, Liang WJ, Yu YD, Anderson L, Wang M, Xu RH, Wu XW, Zheng HY, Chen JD, Liang G, Gao Y, Liao M, Fang L, Jiang LY, Li H, Chen F, Di B, He LJ, Lin JY, Tong S, Kong X, Du L, Hao P, Tang H, Bernini A, Yu XJ, Spiga O, Guo ZM, Pan HY, He WZ, Manuguerra JC, Fontanet A, Danchin A, Niccolai N, Li YX, Wu CI, Zhao GP. Cross-host

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A. 2005;102(7):2430-5. https://doi.org/10.1073/pnas.0409608102.

158. Song F, Nannan Shi, Fei Shan, Zhiyong Zhang, Jie Shen, Hongzhou Lu, Yun Ling, Yebin Jiang, Yuxin Shi 2020. Emerging Coronavirus 2019-nCoV Pneumonia. Radiology. In Press.

159. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association. An update on the epidemiological characteristics of novel coronavirus pneumonia（COVID-19. Zhonghua Liu Xing Bing Xue Za Zhi 2020; 41(2):139-144. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.002.

160. Stein RA. The 2019 Coronavirus: Learning Curves, Lessons, and the Weakest Link. Int J Clin Pract. 2020:e13488. https://doi.org/10.1111/ijcp.13488.

161. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y, Gao GF. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol 2016;24(6):490-502. https://doi.org/10.1016/j.tim.2016.03.003.

162. Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection. J Med Virol 2020;10.1002/jmv.25735. https://doi.org/10.1002/jmv.25735.

163. Suzuki T, Otake Y, Uchimoto S, Hasebe A, Goto Y. Genomic Characterization and Phylogenetic Classification of Bovine Coronaviruses Through Whole Genome Sequence Analysis. Viruses 2020;12(2):E183. https://doi.org/10.3390/v12020183.

164. Tang N, Li D, Wang X, Sun Z. Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020a; 10.1111/jth.14768. https://doi.org/10.1111/jth.14768.

165. Tang HS, Yao ZQ, Wang WM. Emergency management of prevention and control of novel coronavirus pneumonia in departments of stomatology. Zhonghua Kou Qiang Yi Xue Za Zhi 2020b;55(0):E002. https://doi.org/10.3760/cma.j.cn112144-20200205-00037.

166. Tekes G, Thiel HJ. Feline Coronaviruses: Pathogenesis of Feline Infectious Peritonitis. Adv Virus Res 2016;96:193-218. https://doi.org/10.1016/bs.aivir.2016.08.002.

167. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect. 2020;22(2):72-73. doi: 10.1016/j.micinf.2020.02.006.

168. Thompson RN. Novel Coronavirus Outbreak in Wuhan, China, 2020: Intense Surveillance Is Vital for Preventing Sustained Transmission in New Locations. J Clin Med 2020;9(2):E498. https://doi.org/10.3390/jcm9020498.

169. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y, Ying T. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. 2020;9(1):382-385. https://doi.org/10.1080/22221751.2020.1729069.

170. Tian HY. 2019-nCoV: new challenges from coronavirus. Zhonghua Yu Fang Yi Xue Za Zhi. 2020;54(0):E001. Chinese. doi: 10.3760/cma.j.issn.0253-9624.2020.0001.

171. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. 2020. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020. doi: 10.1056/NEJMc2004973.

172. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure and function and antigenicity of the SARS-CoV-2 spike glycoprotein. bioTxiv 2020. 2020.02.19.956581.

173. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 2020;JVI.00127-20. https://doi.org/10.1128/JVI.00127-20.

174. Wang LF, Eaton BT. Bats, civets and the emergence of SARS. Curr Top Microbiol Immunol. 2007;315:325-44. doi: 10.1007/978-3-540-70962-6_13. PMID: 17848070.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

175. Wang N, Li SY, Yang XL, Huang HM, Zhang YJ, Guo H, Luo CM, Miller M, Zhu G, Chmura AA, Hagan E, Zhou JH, Zhang YZ, Wang LF, Daszak P, Shi ZL. Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China. Virol Sin. 2018;33(1):104-7. https://doi.org/10.1007/s12250-018-0012-7.

176. Wang D; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, 2020a. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. doi:10.1001/jama.2020a.1585.

177. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020b. doi: 10.1002/jmv.25748.

178. Wang L, Shi Y, Xiao T, Fu J, Feng X, Mu D, Feng Q, Hei M, Hu X, Li Z, Lu G, Tang Z, Wang Y, Wang C, Xia S, Xu J, Yang Y, Yang J, Zeng M, Zheng J, Zhou W, Zhou X, Zhou X, Du L, Lee SK, Zhou W; Working Committee on Perinatal and Neonatal Management for the Prevention and Control of the 2019 Novel Coronavirus Infection. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (First edition). Ann Transl Med. 2020c;8(3):47. doi: 10.21037/atm.2020.02.20.

179. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol. 2020d;92(4):441-447. doi: 10.1002/jmv.25689.

180. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020e;30(3):269-271. doi: 10.1038/s41422-020-0282-0.

181. Watts CH, Vallance P, Whitty CJM. Coronavirus: global solutions to prevent a pandemic. Nature 2020;578(7795):363. https://doi.org/10.1038/d41586-020-00457-y.

182. WHO. 2003. World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). Available online: https://www.who.int/csr/sars/en/WHOconsensus.pdf (accessed on 29 January 2020).

183. WHO 2020a. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Mission-on-covid-19-final-report.pdf. pp 1-40.

184. WHO. MERS-CoV. 2020b. https://www.who.int/emergencies/merscov/en/ (29 February 2020, date last accessed).

185. WHO. International travel and health. Updated WHO recommendations for international traffic concerning COVID-19 outbreak. 2020c. https://www.who.int/ith/2019-nCoV_advice_for_international_traffic-rev/en/.

186. Wilder-Smith A, Chiew CJ, Lee VJ. 2020. Can we contain the COVID-19 outbreak with the same measures as for SARS? Lancet Infect Dis. pii: S1473-3099(20)30129-8. doi: 10.1016/S1473-3099(20)30129-8.

187. Wilson ME, Chen LH. Travelers Give Wings to Novel Coronavirus (2019-nCoV). J Travel Med. 2020:taaa015. doi: 10.1093/jtm/taaa015.

188. Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, Lau JH, Bai R, Teng JL, Tsang CC, Wang M, Zheng BJ, Chan KH, Yuen KY. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. J Virol 2012;86(7):3995-4008. https://doi.org/10.1128/JVI.06540-11.

189. Wood C. Infections without borders: a new coronavirus in Wuhan, China. Br J Nurs. 2020;29(3):166-167. doi: 10.12968/bjon.2020.29.3.166.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

190. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;eabb2507. https://doi.org/10.1126/science.abb2507.

191. Wu P., X. Hao, E.H.Y. Lau, J.Y. Wong, K.S.M. Leung, J.T. Wu, et al., Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020, Euro Surveill. 25 (2020).

192. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol 2020;10.1002/jmv.25725. https://doi.org/10.1002/jmv.25725.

193. Xiao K, Zhai J, Feng Y, Zhou N, Zhang X, Zou JJ, Li N, Guo Y, Li X, Shen X, Zhang Z, Shu F, Huang W, Li Y, Zhang Z, Chen R-A, Wu Y-J, Peng S-M, Huang M, Xie W-J, Cai Q-H, Hou F-H, Liu Y, Chen W, Xiao L, Shen, Y. 2020. Isolation and characterization of 2019-nCoV-like coronavirus from Malayan Pangolins. bioRxiv 2020.2002.2017.951335. doi:10.1101/2020.02.17.951335.

194. Xu Y. Genetic diversity and potential recombination between ferret coronaviruses from European and American lineages. J Infect 2020;80(3):350-371. https://doi.org/10.1016/j.jinf.2020.01.016.

195. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020a;63(3):457-460. doi: 10.1007/s11427-020-1637-5.

196. Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, Dong L, Ma X, Zhang HJ, Gao BL. Clinical and computed tomographic imaging features of Novel Coronavirus Pneumonia caused by SARS-CoV-2. J Infect 2020b;S0163-4453(20)30100-6. https://doi.org/10.1016/j.jinf.2020.02.017.

197. Xu J, Zhao S, Teng T, Abdalla AE, Zhu W, Xie L, Wang Y, Guo X. 2020c. Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. Viruses. 12(2): 244. doi: 10.3390/v12020244.

198. Yang H, Wang C, Poon LC. Novel coronavirus infection and pregnancy. Ultrasound Obstet Gynecol. 2020 Mar 5. doi: 10.1002/uog.22006.

199. Yee J, Unger L, Zadravecz F, Cariello P, Seibert A, Johnson MA, Fuller MJ. Novel coronavirus 2019 (COVID-19) emergence and implications for emergency care. Journal of American college of Emergency Physicians Open/Early Review. http://doi.org/10.1002/emp2.12034.

200. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020;3. https://doi.org/10.1001/jama.2020.3204.

201. Yu H, Wu JT, Cowling BJ, Liao Q, Fang VJ, Zhou S, Wu P, Zhou H, Lau EH, Guo D, Ni MY, Peng Z, Feng L, Jiang H, Luo H, Li Q, Feng Z, Wang Y, Yang W, Leung GM. Effect of closure of live poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study. Lancet. 2014;383(9916):541-8. doi: 10.1016/S0140-6736(13)61904-2.

202. Zhang XM, Herbst W, Kousoulas KG, Storz J. Biological and genetic characterization of a hemagglutinating coronavirus isolated from a diarrhoeic child. J Med Virol 1994;44(2):152-61. https://doi.org/10.1002/jmv.1890440207.

203. Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. J Med Virol. 2020a. doi: 10.1002/jmv.25742.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

204. Zhang T, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. Curr Biol. 2020b. pii: S0960-9822(20)30360-2. doi: 10.1016/j.cub.2020.03.022.
205. Zhang N, Wang L, Deng X, Liang R, Su M, He C, Hu L, Su Y, Ren J, Yu F, Du L, Jiang S. Recent advances in the detection of respiratory virus infection in humans. J Med Virol. 2020c;92(4):408-417. doi: 10.1002/jmv.25674.
206. Zhang Q, Wang Y, Qi C, Shen L, Li J. Clinical trial analysis of 2019-nCoV therapy registered in China. J Med Virol 2020d;10.1002/jmv.25733. https://doi.org/10.1002/jmv.25733.
207. Zhou P, Fan H, Lan T, Yang XL, Shi WF, Zhang W, Zhu Y, Zhang YW, Xie QM, Mani S, Zheng XS, Li B, Li JM, Guo H, Pei GQ, An XP, Chen JW, Zhou L, Mai KJ, Wu ZX, Li D, Anderson DE, Zhang LB, Li SY, Mi ZQ, He TT, Cong F, Guo PJ, Huang R, Luo Y, Liu XL, Chen J, Huang Y, Sun Q, Zhang XL, Wang YY, Xing SZ, Chen YS, Sun Y, Li J, Daszak P, Wang LF, Shi ZL, Tong YG, Ma JY. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. Nature 2018;556(7700):255-258. https://doi.org/10.1038/s41586-018-0010-9.
208. Zhou W, Liu Y, Tian D, Wang C, Wang S, Cheng J, Hu M, Fang M, Gao Y. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduct Target Ther. 2020a;5:18. doi: 10.1038/s41392-020-0127-9.
209. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother. 2020b:dkaa114. doi: 10.1093/jac/dkaa114.
210. Zhu N., D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A novel coronavirus from patients with pneumonia in China, N. Engl. J. Med. 382 (2020) 727–733, https://doi.org/10.1056/NEJMoa2001017 2020.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at Travel Medicine and Infectious Disease 2020, 37; doi:10.1016/j.tmaid.2020.101830

Figure Legends

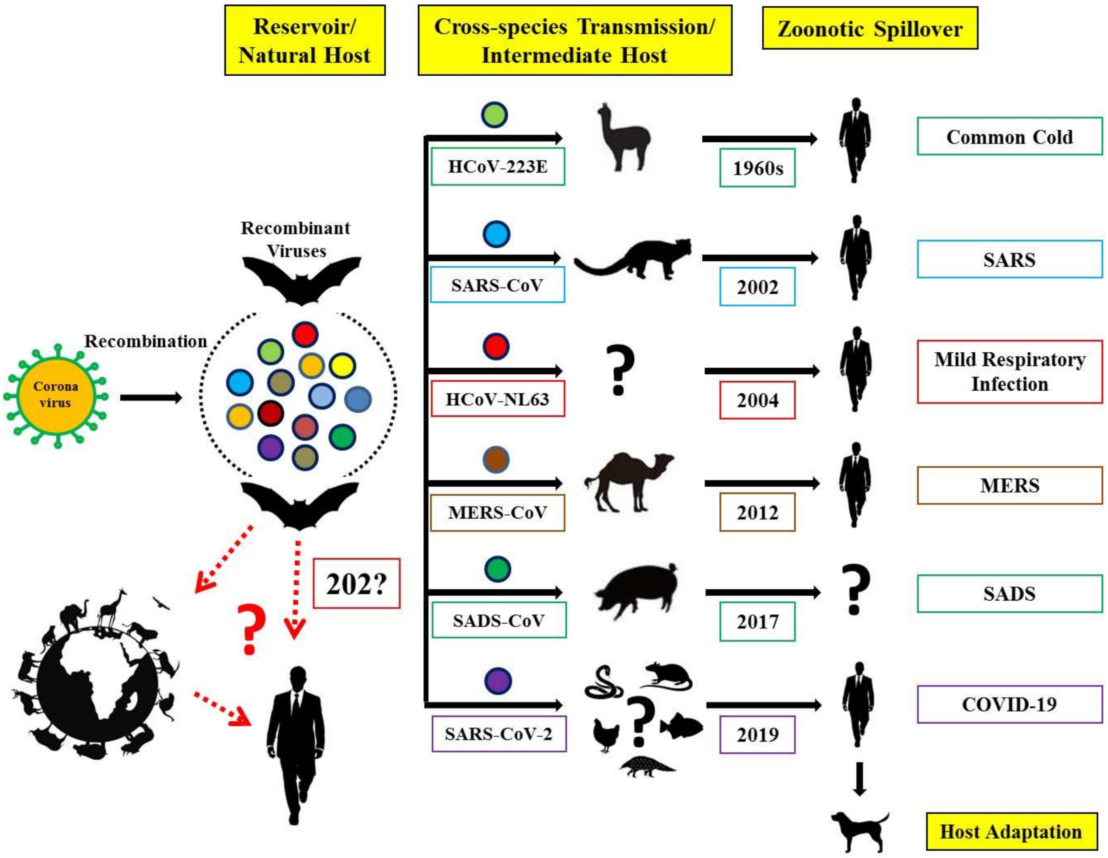

Figure 1: Cross-species transmission of known zoonotic coronaviruses from bats to animals before spillover to humans and probable prospects of further transmission to mammalian hosts.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 April 2020 doi:10.20944/preprints202004.0011.v1

Peer-reviewed version available at *Travel Medicine and Infectious Disease* **2020**, *37*; doi:10.1016/j.tmaid.2020.101830

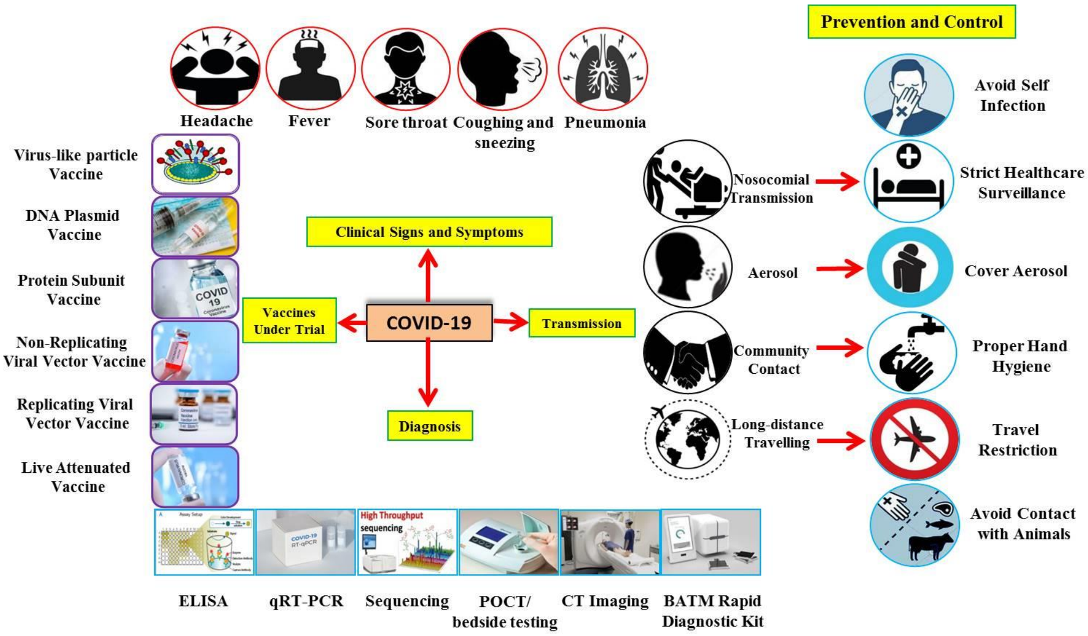

Figure 2: Schematic illustration of clinical signs, modes of transmission, advances in diagnosis and vaccine designing along with salient prevention and control strategies to counter COVID-19.