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challenge with MERS-CoV (169). The intranasal administration of the recombinant adenovirus-based vaccine in BALB/c mice was found to induce long-lasting neutralizing immunity against MERS spike pseudotyped virus, characterized by the induction of systemic IgG, secretory IgA, and lung-resident memory T-cell responses (177). Immunoinformatics methods have been employed for the genome-wide screening of potential vaccine targets among the different immunogens of MERS-CoV (178). The N protein and the potential B-cell epitopes of MERS-CoV E protein have been suggested as immunoprotective targets inducing both T-cell and neutralizing antibody responses (178, 179).

The collaborative effort of the researchers of Rocky Mountain Laboratories and Oxford University is designing a chimpanzee adenovirus-vectored vaccine to counter COVID-19 (180). The Coalition for Epidemic Preparedness Innovations (CEPI) has initiated three programs to design SARS-CoV-2 vaccines (181). CEPI has a collaborative project with Inovio for designing a MERS-CoV DNA vaccine that could potentiate effective immunity. CEPI and the University of Queensland are designing a molecular clamp vaccine platform for MERS-CoV and other pathogens, which could assist in the easier identification of antigens by the immune system (181). CEPI has also funded Moderna to develop

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appeared asymptomatic[45]. Another serological study detected SARS-CoV-2 neutralizing antibodies in cat serum samples collected in Wuhan after the COVID-19 outbreak, providing evidence for SARS-CoV-2 infectionin cat populations in Wuhan, although the potential of SARS-CoV-2 transmission from cats to humans is currently uncertain[46].

Receptor use and pathogenesis

SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2)[11,47]. Besides human ACE2 (hACE2), SARS-CoV-2 also recognizes ACE2 from pig, ferret, rhesus monkey, civet, cat, pan-golin, rabbit and dog[11,43,48,49]. The broad receptor usage of SARS-CoV-2 implies that it may have a wide host range, and the varied efficiency of ACE2 usage in different animals may indicate their different susceptibilities to SARS-CoV-2 infection. The S1 subunit of a coronavirus is further divided into two functional domains, an N-terminal domain and a C-terminal domain.
Structural and biochemical analyses identified a 211 amino acid region (amino acids 319–529) at the S1C-terminal domain of SARSCoV-2 as the RBD, which has a key role in virus entry and is the target of neutralizing antibodies[50,51] (FIG. 3a). The RBD mediates contact with the ACE2 receptor (amino acids 437–507 of SARS-CoV-2 S protein), and this region in SARS-CoV-2 differs from that in SARS-CoV in the five residues crit-

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fever, cough, and sputum (83). Hence, the clinicians must be on the look-out for the possible occurrence of atypical clinical manifestations to avoid the possibility of missed diagnosis. The early transmission ability of SARS-CoV-2 was found to be similar to or slightly higher than that of SARS-CoV, reflecting that it could be controlled despite moderate to high transmissibility (84).

Increasing reports of SARS-CoV-2 in sewage and wastewater warrants the need for further investigation due to the possibility of fecal-oral transmission. SARS-CoV-2 present in environmental compartments such as soil and water will finally end up in the wastewater and sewage sludge of treatment plants (328). Therefore, we have to reevaluate the current wastewater and sewage sludge treatment procedures and introduce advanced techniques that are specific and effective against SARS-CoV-2. Since there is active shedding of SARS-CoV-2 in the stool, the prevalence of infections in a large population can be studied using wastewater-based epidemiology. Recently, reverse transcription-quantitative PCR (RT-qPCR) was used to enumerate the copies of SARS-CoV-2 RNA concentrated from wastewater collected from a wastewater treatment plant (327). The calculated viral RNA copy numbers determine the number of infected individuals. The

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explored targeting molecular dynamic simulations, evaluating their interaction with corresponding major histocompatibility complex class I molecules. They potentially induce immune responses (176). The recombinant vaccine can be designed by using rabies virus (RV) as a viral vector. RV can be made to express MERS-CoV S1 protein on its surface so that an immune response is induced against MERS-CoV. The RV vector-based vaccines against MERS-CoV can induce faster antibody response as well as higher degrees of cellular immunity than the Gram-positive enhancer matrix (GEM) particle vaccine vector-based vaccine. However, the latter can induce a very high antibody response at lower doses (167). Hence, the degree of humoral and cellular immune responses produced by such vaccines depends upon the vector used.

Dual vaccines have been getting more popular recently. Among them, the rabies virus-based vectored vaccine platform is used to develop vaccines against emerging infectious diseases. The dual vaccine developed from inactivated rabies virus particles that express the MERS-CoV S1 domain of S protein was found to induce immune responses for both MERS-CoV and rabies virus. The vaccinated mice were found to be completely protected from challenge with MERS-CoV (169). The intranasal

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specimens, like bronchoalveolar lavage fluid, sputum, nasal swabs, fibrobronchoscope brush biopsy specimens, pharyngeal swabs, feces, and blood (246).

The presence of SARS-CoV-2 in fecal samples has posed grave public health concerns. In addition to the direct transmission mainly occurring via droplets of sneezing and coughing, other routes, such as fecal excretion and environmental and fomite contamination, are contributing to SARS-CoV-2 transmission and spread (249–252). Fecal excretion has also been documented for SARS-CoV and MERS-CoV, along with the potential to stay viable in situations aiding fecal-oral transmission. Thus, SARS-CoV-2 has every possibility to be transmitted through this mode. Fecal-oral transmission of SARS-CoV-2, particularly in regions having low standards of hygiene and poor sanitation, may have grave consequences with regard to the high spread of this virus. Ethanol and disinfectants containing chlorine or bleach are effective against coronaviruses (249–252). Appropriate precautions need to be followed strictly while handling the stools of patients infected with SARS-CoV-2. Biowaste materials and sewage from hospitals must be adequately disinfected, treated, and disposed of properly. The significance of frequent and good hand hygiene and

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Currently, our knowledge on the animal origin of SARS-CoV-2 remains incomplete to a large part. The reservoir hosts of the virus have not been clearly proven. It is unknown whether SARS-CoV-2 was transmitted to humans through an intermediate host and which animals may act as its intermediate host. Detection of RaTG13, RmYN02 and pangolin coronaviruses implies that diverse coronaviruses similar to SARS-CoV-2 are circulating in wildlife. In addition, as previous studies showed recombination as the potential origin of some sarbecoviruses such as SARS-CoV, it cannot be excluded that viral RNA recombination among different related coronaviruses was involved in the evolution of SARS-CoV-2. Extensive surveillance of SARS-CoV-2-related viruses in China, Southeast Asia and other regions targeting bats, wild and captured pangolins and other wildlife species will help us to better understand the zoonotic origin of SARS-CoV-2.

Besides wildlife, researchers investigated the susceptibility of domesticated and laboratory animals to SARS-CoV-2 infection. The study demonstrated experimentally that SARS-CoV-2 replicates efficiently in cats and in the upper respiratory tract of ferrets, whereas dogs, pigs, chickens and ducks were not susceptible to SARS-CoV-2 (REF.[43]). The susceptibility of minks was documented by a report from the Netherlands on an outbreak of SARS-CoV-2 infection in farmed minks. Although the symptoms in most infected minks were mild, some developed severe respiratory distress and died of interstitial pneumonia[44]. Both virological and serological testing found transmission of SARS-CoV-2 infection in two dogs from households with human cases of COVID-19 in Hong Kong, but the dogs

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proteins without the presence of S protein would not confer any noticeable protection, with the absence of detectable serum SARS-CoV-neutralizing antibodies (170). Antigenic determinant sites present over S and N structural proteins of SARS-CoV-2 can be explored as suitable vaccine candidates (294). In the Asian population, S, E, M, and N proteins of SARS-CoV-2 are being targeted for developing subunit vaccines against COVID-19 (295).

The identification of the immunodominant region among the subunits and domains of S protein is critical for developing an effective vaccine against the coronavirus. The C-terminal domain of the S1 subunit is considered the immunodominant region of the porcine deltacoronavirus S protein (171). Similarly, further investigations are needed to determine the immunodominant regions of SARS-CoV-2 for facilitating vaccine development.

However, our previous attempts to develop a universal vaccine that is effective for both SARS-CoV and MERS-CoV based on T-cell epitope similarity pointed out the possibility of cross-reactivity among coronaviruses (172). That can be made possible by selected potential vaccine targets that are common to both viruses. SARS-CoV-2 has been reported to be closely related to SARS-CoV (173, 174). Hence, knowledge and understanding of

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The exploration of fully human antibodies (human single-chain antibodies; HuscFvs) or humanized nanobodies (single-domain antibodies; sdAb, VH/VHH) could aid in blocking virus replication, as these agents can traverse the virus-infected cell membranes (transbodies) and can interfere with the biological characteristics of the replicating virus proteins. Such examples include transbodies to the influenza virus, hepatitis C virus, Ebola virus, and dengue virus (206). Producing similar transbodies against intracellular proteins of coronaviruses, such as papain-like proteases (PLpro), cysteine-like protease (3CLpro), or other nsps, which are essential for replication and transcription of the virus, might formulate a practical move forward for a safer and potent passive immunization approach for virus-exposed persons and rendering therapy to infected patients.

In a case study on five grimly sick patients having symptoms of severe pneumonia due to COVID-19, convalescent plasma administration was found to be helpful in patients recovering successfully. The convalescent plasma containing a SARS-CoV-2-specific ELISA (serum) antibody titer higher than 1:1,000 and neutralizing antibody titer more significant than 40 was collected from the recovered patients and used for plasma transfusion

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another study, the average reproductive number of COVID-19 was found to be 3.28, which is significantly higher than the initial WHO estimate of 1.4 to 2.5 (77). It is too early to obtain the exact R_0 value, since there is a possibility of bias due to insufficient data. The higher R_0 value is indicative of the more significant potential of SARS-CoV-2 transmission in a susceptible population. This is not the first time where the culinary practices of China have been blamed for the origin of novel coronavirus infection in humans. Previously, the animals present in the live-animal market were identified to be the intermediate hosts of the SARS outbreak in China (78). Several wildlife species were found to harbor potentially evolving coronavirus strains that can overcome the species barrier (79). One of the main principles of Chinese food culture is that live-slaughtered animals are considered more nutritious (5).

After 4 months of struggle that lasted from December 2019 to March 2020, the COVID-19 situation now seems under control in China. The wet animal markets have reopened, and people have started buying bats, dogs, cats, birds, scorpions, badgers, rabbits, pangolins (scaly anteaters), minks, soup from palm civet, ostriches, hamsters, snapping turtles, ducks, fish, Siamese crocodiles, and other

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fatigue. Individuals with asymptomatic and atypical clinical manifestations were also identified recently, further adding to the complexity of disease transmission dynamics. Atypical clinical manifestations may only express symptoms such as fatigue instead of respiratory signs such as fever, cough, and sputum. In such cases, the clinician must be vigilant for the possible occurrence of asymptomatic and atypical clinical manifestations to avoid the possibility of missed diagnoses.

The present outbreak caused by SARS-CoV-2 was, indeed, expected. Similar to previous outbreaks, the current pandemic also will be contained shortly. However, the real question is, how are we planning to counter the next zoonotic CoV epidemic that is likely to occur within the next 5 to 10 years or perhaps sooner? Our knowledge of most of the bat CoVs is scarce, as these viruses have not been isolated and studied, and extensive studies on such viruses are typically only conducted when they are associated with specific disease outbreaks. The next step following the control of the COVID-19 outbreak in China should be focused on screening, identification, isolation, and characterization of CoVs present in wildlife species of China, particularly in bats. Both in vitro and in vivo studies (using suitable animal models) should be conducted

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category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should undergo regular decontamination preferably with sodium hypochlorite. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as intubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for atleast 3 d and have two consecutive negative molecular tests at 1 d sampling interval. This recommendation is different from pandemic flu where patients were

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patients with COVID-19 can be found on the WHO and CDC websites.[67]

16 CONCLUSION

The corona virus (COVID-19) spreads at an alarming rate all over the world. The outbreak of the virus has confronted the world's economic, medical and public health infrastructure. Elderly and immunocompromised patients also are susceptible to the virus's mortal impacts. Currently, there is no documented cure for the virus and no vaccine has been created, although some treatment protocols have been promising. Therefore, the virus can be controlled with the appropriate prevention strategies. Also, attempts have to be made to formulate systematic strategies to prevent such future zoonotic outbreaks.

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a polybasic cleavage site (RRAR), which enables effective cleavage by furin and other proteases[27]. Such an S1–S2 cleavage site is not observed in all related viruses belonging to the subgenus Sarbecovirus, except for a similar three amino acid insertion (PAA) in RmYN02, a bat-derived coronavirus newly reported from *Rhinolophus malayanus* in China[28] (FIG. 3a). Although the insertion in RmYN02 does not functionally represent a polybasic cleavage site, it provides support for the notion that this characteristic, initially considered unique to SARS-CoV-2, has been acquired naturally[28]. A structural study suggested that the furin-cleavage site can reduce the stability of SARS-CoV-2 S protein and facilitate the conformational adaptation that is required for the binding of the RBD to its receptor[29]. Whether the higher transmissibility of SARS-CoV-2 compared with SARS-CoV is a gain of function associated with acquisition of the furin-like cleavage site is yet to be demonstrated[26].

An additional distinction is the accessory gene *orf8* of SARS-CoV-2, which encodes a novel protein showing only 40% amino acid identity to ORF8 of SARS-CoV. Unlike in SARS-CoV, this new ORF8 protein does not contain a motif that triggers intracellular stress pathways[25]. Notably, a SARS-CoV-2 variant with a 382-nucleotide deletion covering the whole of ORF8 has been discovered in a number of patients in Singapore, which resembles the 29- or 415-nucleotide deletions in the ORF8 regions observed in human SARS-CoV variants from the late phase of the 2002–2003 outbreak[30]. Such ORF8 deletion variants seem to be involved in the fast across-species transmission from an animal host.

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therapeutics, and drug regimens to counter emerging viruses (161–163, 280). Several attempts are being made to design and develop vaccines for CoV infection, mostly by targeting the spike glycoprotein. Nevertheless, owing to extensive diversity in antigenic variants, cross-protection rendered by the vaccines is significantly limited, even within the strains of a phylogenetic subcluster (104). Due to the lack of effective antiviral therapy and vaccines in the present scenario, we need to depend solely on implementing effective infection control measures to lessen the risk of possible nosocomial transmission (68). Recently, the receptor for SARS-CoV-2 was established as the human angiotensin-converting enzyme 2 (hACE2), and the virus was found to enter the host cell mainly through endocytosis. It was also found that the major components that have a critical role in viral entry include PIKfyve, TPC2, and cathepsin L. These findings are critical, since the components described above might act as candidates for vaccines or therapeutic drugs against SARS-CoV-2 (293).

The majority of the treatment options and strategies that are being evaluated for SARS-CoV-2 (COVID-19) have been taken from our previous experiences in treating SARS-CoV, MERS-CoV, and other emerging viral diseases. Several therapeutic

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4 VIROLOGY

Coronaviruses, a family of viruses within the nidoviruses superfamily, are further classified according to their genera, alpha-, beta-, gamma- and deltacoronaviruses (α-, β-, γ- and δ-). Among those, alpha and beta species are capable of contaminating only mammals, whereas the other two genera can infect birds and could also infect mammals.[13,14] Two of these genera belong to human coronaviruses (HCoVs): α-coronaviruses, which comprise human coronavirus 229E (hcov229E) and human coronavirus NL63 (hcovNL63), and β-coronaviruses, which are human coronavirus HKU1, human coronavirus OC43, MERS-CoV (known as Middle East respiratory syndrome coronavirus) and SARS-CoV (referred to as severe acute respiratory syndrome coronavirus).[15]

The severe acute respiratory syndrome CoV-2 (SARS-CoV-2) is now named novel COVID-19 (coronavirus disease 2019).[16] Genome sequencing and phylogenetic research revealed that the COVID-19-causing coronavirus is a beta-coronavirus that belongs to the same subtypes as SARS virus, but represents a new variant group. The receptor-binding gene region

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The pathogenesis of SARS-CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure. On binding to epithelial cells in the respiratory tract, SARS-CoV-2 starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs. The rapid replication of SARS-CoV-2 in the lungs may trigger a strong immune response. Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure, which is considered the main cause of death in patients with COVID-19 (REFS[60,61]). Patients of older age (≥60 years) and with serious pre-existing diseases have a greater risk of developing acute respiratory distress syndrome and death[62-64] (FIG. 4). Multiple organ failure has also been reported in some COVID-19 cases[9,13,65].

Histopathological changes in patients with COVID-19 occur mainly in the lungs. Histopathology analyses showed bilateral diffused alveolar damage, hyaline membrane formation, desquamation of pneumocytes and fibrin deposits in lungs of patients with severe COVID-19. Exudative inflammation was also observed in some cases. Immunohistochemistry assays detected SARS-CoV-2 antigen in the upper airway, bronchial epithelium and submucosal gland epithelium, as well as in type I and type II pneumocytes, alveolar macrophages and hyaline membranes in the lungs[13,60,6467].

Animal models used for studying SARS-CoV-2 infection pathogenesis include non-human primates (rhesus macaques, cynomolgus monkeys, marmosets and African green monkeys), mice (wild-type mice (with mouse-adapted virus) and human ACE2-transgenic or human ACE2-knock-in mice), ferrets and golden hamsters[43,48,68–74]. In non-human primate models, most species display clinical features similar to patients with COVID-19, including strong shedding, virus replication and host response to SARS-CoV-2 infection[69,72,73]. For example, in the rhesus macaque model, high viral loads were detected in the upper and

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Even though a high similarity has been reported between the genome sequence of the new coronavirus (SARS-CoV-2) and SARS-like CoVs, the comparative analysis recognized a furin-like cleavage site in the SARS-CoV-2 S protein that is missing from other SARS-like CoVs (99). The furin-like cleavage site is expected to play a role in the life cycle of the virus and disease pathogenicity and might even act as a therapeutic target for furin inhibitors. The highly contagious nature of SARS-CoV-2 compared to that of its predecessors might be the result of a stabilizing mutation that occurred in the endosome-associated-protein-like domain of nsp2 protein.

Similarly, the destabilizing mutation near the phosphatase domain of nsp3 proteins in SARS-CoV-2 could indicate a potential mechanism that differentiates it from other CoVs (100). Even though the CFR reported for COVID-19 is meager compared to those of the previous SARS and MERS outbreaks, it has caused more deaths than SARS and MERS combined (101). Possibly related to the viral pathogenesis is the recent finding of an 832-nucleotide (nt) deletion in ORF8, which appears to reduce the replicative fitness of the virus and leads to attenuated phenotypes of SARS-CoV-2 (256).

Coronavirus is the most prominent example of a

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was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths. One case of severe pneumonia and multiorgan dysfunction in a child has also been reported [19]. Similarly the neonatal cases that have been reported have been mild [20].

Diagnosis [21]

A suspect case is defined as one with fever, sore throat and cough who has history of travel to China or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed

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trimeric S1 locates itself on top of the trimeric S2 stalk (45). Recently, structural analyses of the S proteins of COVID-19 have revealed 27 amino acid substitutions within a 1,273-amino-acid stretch (16). Six substitutions are located in the RBD (amino acids 357 to 528), while four substitutions are in the RBM at the CTD of the S1 domain (16). Of note, no amino acid change is seen in the RBM, which binds directly to the angiotensin-converting enzyme-2 (ACE2) receptor in SARS-CoV (16, 46). At present, the main emphasis is knowing how many differences would be required to change the host tropism. Sequence comparison revealed 17 nonsynonymous changes between the early sequence of SARS-CoV-2 and the later isolates of SARS-CoV. The changes were found scattered over the genome of the virus, with nine substitutions in ORF1ab, ORF8 (4 substitutions), the spike gene (3 substitutions), and ORF7a (single substitution) (4). Notably, the same nonsynonymous changes were found in a familial cluster, indicating that the viral evolution happened during person-to-person transmission (4, 47). Such adaptive evolution events are frequent and constitute a constantly ongoing process once the virus spreads among new hosts (47). Even though no functional changes occur in the virus associated with this adaptive evolution, close monitoring of the viral

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Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan [17]. Similarly, the severity and case fatality rate in patients outside China has been reported to be milder [6]. This may either be due to selection bias wherein the cases reporting from Wuhan included only the severe cases or due to predisposition of the Asian population to the virus due to higher expression of ACE_2 receptors on the respiratory mucosa [11].

Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females. The median age was 8 y 11 mo and in 28 children the infection was linked to a family member and 26

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new targeted drugs, and prevention of further epidemics (13). The most common symptoms associated with COVID-19 are fever, cough, dyspnea, expectoration, headache, and myalgia or fatigue.

In contrast, less common signs at the time of hospital admission include diarrhea, hemoptysis, and shortness of breath (14). Recently, individuals with asymptomatic infections were also suspected of transmitting infections, which further adds to the complexity of disease transmission dynamics in COVID-19 infections (1). Such efficient responses require in-depth knowledge regarding the virus, which currently is a novel agent; consequently, further studies are required.

Comparing the genome of SARS-CoV-2 with that of the closely related SARS/SARS-like CoV revealed that the sequence coding for the spike protein, with a total length of 1,273 amino acids, showed 27 amino acid substitutions. Six of these substitutions are in the region of the receptor-binding domain (RBD), and another six substitutions are in the underpinning subdomain (SD) (16). Phylogenetic analyses have revealed that SARS-CoV-2 is closely related (88% similarity) to two SARS-like CoVs derived from bat SARS-like CoVs (bat-SL-CoVCZ45 and bat-SL-CoVZXC21) (Fig. 1).

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prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated. Mechanical ventilation and even extra corporeal membrane oxygen support may be needed. Renal replacement therapy may be needed in some. Antibiotics and antifungals are required if co-infections are suspected or proven. The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS [24, 25]. Detailed guidelines for critical care management for COVID-19 have been published by the WHO [26]. There is, as of now, no approved treatment for COVID-19. Antiviral drugs such as ribavirin, lopinavir-ritonavir have been used based on the experience with SARS and MERS. In a historical

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Princess, Celebrity Apex, and Ruby Princess. The number of confirmed COVID-19 cases around the world is on the rise. The success of preventive measures put forward by every country is mainly dependent upon their ability to anticipate the approaching waves of patients. This will help to properly prepare the health care workers and increase the intensive care unit (ICU) capacity (321). Instead of entirely relying on lockdown protocols, countries should focus mainly on alternative intervention strategies, such as large-scale testing, contract tracing, and localized quarantine of suspected cases for limiting the spread of this pandemic virus. Such intervention strategies will be useful either at the beginning of the pandemic or after lockdown relaxation (322). Lockdown should be imposed only to slow down disease progression among the population so that the health care system is not overloaded.

The reproduction number (R_0) of COVID-19 infection was earlier estimated to be in the range of 1.4 to 2.5 (70); recently, it was estimated to be 2.24 to 3.58 (76). Compared to its coronavirus predecessors, COVID-19 has an R_0 value that is greater than that of MERS ($R_0 < 1$) (108) but less than that of SARS (R_0 value of 2 to 5) (93). Still, to prevent further spread of disease at mass gatherings,

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Some therapeutic options for treating COVID-19 showed efficacy in *in vitro* studies; however, to date, these treatments have not undergone any randomized animal or human clinical trials, which limit their practical applicability in the current pandemic (7, 9, 19–21).

The present comprehensive review describes the various features of SARS-CoV-2/COVID-19 causing the current disease outbreaks and advances in diagnosis and developing vaccines and therapeutics. It also provides a brief comparison with the earlier SARS and MERS CoVs, the veterinary perspective of CoVs and this emerging novel pathogen, and an evaluation of the zoonotic potential of similar CoVs to provide feasible One Health strategies for the management of this fatal virus (22–367).

THE VIRUS (SARS-CoV-2)

Coronaviruses are positive-sense RNA viruses having an extensive and promiscuous range of natural hosts and affect multiple systems (23, 24). Coronaviruses can cause clinical diseases in humans that may extend from the common cold to more severe respiratory diseases like SARS and MERS (17, 279). The recently emerging SARS-CoV-2 has wrought havoc in China and caused a pandemic situation in the worldwide population leading to

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responsible for MERS-CoV and SARS-CoV (3). The newly emerged SARS-CoV-2 is a group 2B coronavirus (2). The genome sequences of SARS-CoV-2 obtained from patients share 79.5% sequence similarity to the sequence of SARS-CoV (63).

As of 13 May 2020, a total of 4,170,424 confirmed cases of COVID-19 (with 287,399 deaths) have been reported in more than 210 affected countries worldwide (WHO Situation Report 114

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Coronavirus S protein is a large, multifunctional class I viral transmembrane protein. The size of this abundant S protein varies from 1,160 amino acids (IBV, infectious bronchitis virus, in poultry) to 1,400 amino acids (FCoV, feline coronavirus) (43). It lies in a trimer on the virion surface, giving the virion a corona or crown-like appearance. Functionally it is required for the entry of the infectious virion particles into the cell through interaction with various host cellular receptors (44).

Furthermore, it acts as a critical factor for tissue tropism and the determination of host range (45). Notably, S protein is one of the vital immunodominant proteins of CoVs capable of inducing host immune responses (45). The ectodomains in all CoVs S proteins have similar domain organizations, divided into two subunits, S1 and S2 (43). The first one, S1, helps in host receptor binding, while the second one, S2, accounts for fusion. The former (S1) is further divided into two subdomains, namely, the N-terminal domain (NTD) and C-terminal domain (CTD). Both of these subdomains act as receptor-binding domains, interacting efficiently with various host receptors (45). The S1 CTD contains the receptor-binding motif (RBM). In each coronavirus spike protein, the trimeric S1 locates on top of the trimeric S2

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Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans. In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory illness, making emerging coronaviruses a new public health concern in the twenty-first century[1]. At the end of 2019, a novel coronavirus designated as SARS-CoV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pneumonia. Being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world[2,3]. It has overwhelmingly surpassed SARS and MERS in terms of both the number of infected people and the spatial range of epidemic areas. The ongoing outbreak of COVID-19 has posed an extraordinary threat to global health[4,5]. In this Review, we summarize the current understanding of the nature of SARS-CoV-2 and COVID-19. On the basis of recently published findings, this comprehensive Review covers the basic biology of SARS-CoV-2, including the genetic characteristics, the potential zoonotic origin and its receptor binding. Furthermore, we will discuss the clinical and epidemiological features, diagnosis of and countermeasures against COVID-19.

Emergence and spread

In late December 2019, several health facilities in Wuhan, in Hubei province in China, reported clusters of patients with pneumonia of unknown cause[6]. Similarly to patients with SARS and MERS, the patients showed symptoms of viral pneumonia, including fever, cough

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it had spread massively to all 34 provinces of China. The number of confirmed cases suddenly increased, with thousands of new cases diagnosed daily during late January[15]. On 30 January, the WHO declared the novel coronavirus outbreak a public health emergency of international concern[16]. On 11 February, the International Committee on Taxonomy of Viruses named the novel coronavirus 'SARS-CoV-2', and the WHO named the disease 'COVID-19' (REF.[17]).

The outbreak of COVID-19 in China reached an epidemic peak in February. According to the National Health Commission of China, the total number of cases continued to rise sharply in early February at an average rate of more than 3,000 newly confirmed cases per day. To control COVID-19, China implemented unprecedentedly strict public health measures. The city of Wuhan was shut down on 23 January, and all travel and transportation connecting the city was blocked. In the following couple of weeks, all outdoor activities and gatherings were restricted, and public facilities were closed in most cities as well as in countryside[18]. Owing to these measures, the daily number of new cases in China started to decrease steadily[19].

However, despite the declining trend in China, the international spread of COVID-19 accelerated from late February. Large clusters of infection have been reported from an increasing number of countries[11]. The high transmission efficiency of SARS-CoV-2 and the abundance of international travel enabled rapid worldwide spread of COVID-19. On 11 March 2020, the WHO officially characterized the global COVID-19 outbreak as a pandemic[20]. Since March, while COVID-19 in China has become effectively controlled, the case numbers in Europe, the USA and other regions have jumped sharply. According to the COVID-19 database shared by the Center for System Science and Engineering at Johns Hopkins University, as of 11 August 2020,

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It is also evident that remdesivir was effective in treating the patients who were infected with Ebola virus. Per this evidence, China has already started testing the efficacy of remdesivir in treating the patients with COVID-19, especially in Wuhan, where the outbreak occurred. Chloroquine, which is an existing drug which is currently used in treating malaria cases, was given to more than 100 patients who were affected with novel coronavirus to test its efficacy.[62]

A multicentric study was conducted in China to test the effectiveness of remdesivir in treating the patients with COVID-19. Thus, the results of the clinical trial proved that remdesivir has a considerably acceptable level of efficacy for treating the patients with COVID-19. Therefore, the National Health Commission of the People's Republic of China decided to include remdesivir in the Guidelines for the Prevention, Diagnosis and Treatment of Pneumonia Caused by COVID-19.[62]

Chloroquine and hydroxychloroquine are existing anti-malaria drugs also given to more than 30 patients infected with COVID-19 in Guangdong province and Hunan province to test their effectiveness and efficacy. Thus, the results of the clinical trial showed that the

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Furthermore, SARS-CoV-2 is genetically distinct from SARS-CoV (79% similarity) and MERS-CoV (nearly 50%) (17). COVID-19 is associated with afflictions of the lungs in all cases and generated characteristic chest computer tomography findings, such as the presence of multiple lesions in lung lobes that appear as dense, ground-glass opaque structures that occasionally coexist with consolidation shadows (18).

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RBD, indicating its potential as a therapeutic agent in the management of COVID-19. It can be used alone or in combination with other effective neutralizing antibodies for the treatment and prevention of COVID-19 (202). Furthermore, SARS-CoV-specific neutralizing antibodies, like m396 and CR3014, failed to bind the S protein of SARS-CoV-2, indicating that a particular level of similarity is mandatory between the RBDs of SARS-CoV and SARS-CoV-2 for the cross-reactivity to occur.

Further assessment is necessary before confirming the effectiveness of such combination therapy. In addition, to prevent further community and nosocomial spread of COVID-19, the postprocedure risk management program should not be neglected (309). Development of broad-spectrum inhibitors against the human coronaviral pathogens will help to facilitate clinical trials on the effectiveness of such inhibitors against endemic and emerging coronaviruses (203). A promising animal study revealed the protective effect of passive immunotherapy with immune serum from MERS-immune camels on mice infected with MERS-CoV (204). Passive immunotherapy using convalescent plasma is another strategy that can be used for treating COVID-19-infected, critically ill patients (205).

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Variant group.The receptor-binding gene region appears to be very similar to that of the SARS-CoV and it is believed that the same receptor would be used for cell entry.[17]

4.1 Virion structure and its genome

Coronaviruses are structurally enveloped, belonging to the positive-strand RNA viruses category that has the largest known genomes of RNA. The structures of the coronavirus are more spherical in shape, but their structure has the potential to modify their morphology in response to environmental conditions, being pleomorphic. The capsular membrane which represents the outer envelope usually has glycoprotein projection and covers the nucleus, comprising a matrix protein containing a positive-strand RNA. Since the structure possesses 5′-capped and 3′-polyadenylated ends, it remains identical to the cellular mRNAs.[18] The structure is comprised of hemagglutinin esterase (HE) (present only in some beta-coronaviruses), spike (S), small membrane (E), membrane (M) and nucleocapsid (N), as shown (Figure 1). The envelope containing glycoprotein is responsible for attachment to the host cell, which possesses the primary anti-genic epitopes mainly those

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range of hosts, producing symptoms and diseases ranging from the common cold to severe and ultimately fatal illnesses, such as SARS, MERS, and, presently, COVID-19. SARS-CoV-2 is considered one of the seven members of the CoV family that infect humans (3), and it belongs to the same lineage of CoVs that causes SARS; however, this novel virus is genetically distinct. Until 2020, six CoVs were known to infect humans, including human CoV 229E (HCoV-229E), HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV. Although SARS-CoV and MERS-CoV have resulted in outbreaks with high mortality, others remain associated with mild upper-respiratory-tract illnesses (4).

Newly evolved CoVs pose a high threat to global public health. The current emergence of COVID-19 is the third CoV outbreak in humans over the past 2 decades (5). It is no coincidence that Fan et al. predicted potential SARS- or MERS-like CoV outbreaks in China following pathogen transmission from bats (6). COVID-19 emerged in China and spread rapidly throughout the country and, subsequently, to other countries. Due to the severity of this outbreak and the potential of spreading on an international scale, the WHO declared a global health emergency on 31 January 2020

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From experience with several outbreaks associated with known emerging viruses, higher pathogenicity of a virus is often associated with lower transmissibility. Compared to emerging viruses like Ebola virus, avian H7N9, SARS-CoV, and MERS-CoV, SARS-CoV-2 has relatively lower pathogenicity and moderate transmissibility (15). The risk of death among individuals infected with COVID-19 was calculated using the infection fatality risk (IFR). The IFR was found to be in the range of 0.3% to 0.6%, which is comparable to that of a previous Asian influenza pandemic (1957 to 1958) (73, 277).

Notably, the reanalysis of the COVID-19 pandemic curve from the initial cluster of cases pointed to considerable human-to-human transmission. It is opined that the exposure history of SARS-CoV-2 at the Wuhan seafood market originated from human-to-human transmission rather than animal-to-human transmission (74); however, in light of the zoonotic spillover in COVID-19, is too early to fully endorse this idea (1). Following the initial infection, human-to-human transmission has been observed with a preliminary reproduction number (R_0) estimated of 1.4 to 2.5 (70, 75), and later it is estimated to be 2.24 to 3.58 (76). In another study, the average reproductive number of

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markers predicted amino acid mutations that resulted in the epidemic strain (104). Transmission can also occur directly from the reservoir host to humans without RBD adaptations. The bat coronavirus that is currently in circulation maintains specific “poised” spike proteins that facilitate human infection without the requirement of any mutations or adaptations (105). Altogether, different species of bats carry a massive number of coronaviruses around the world (106).

The high plasticity in receptor usage, along with the feasibility of adaptive mutation and recombination, may result in frequent interspecies transmission of coronaviruses from bats to animals and humans (106). The pathogenesis of most bat coronaviruses is unknown, as most of these viruses are not isolated and studied (4). Hedgehog coronavirus HKU31, a Betacoronavirus, has been identified from and near hedgehogs in China. Studies show that hedgehogs are the reservoir of Betacoronavirus, and there is evidence of recombination (107).

The current scientific evidence available on MERS infection suggests that the significant reservoir host, as well as the animal source of MERS infection in humans, is the dromedary camels (97). The infected dromedary may not show any visible signs of infection, making it challenging to

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absence of this protein is related to the altered virulence of coronaviruses due to changes in morphology and tropism (54). The E protein consists of three domains, namely, a short hydrophilic amino terminal, a large hydrophobic transmembrane domain, and an efficient C-terminal domain (51). The SARS-CoV-2 E protein reveals a similar amino acid constitution without any substitution (16).

N Protein

The N protein of coronavirus is multipurpose. Among several functions, it plays a role in complex formation with the viral genome, facilitates M protein interaction needed during virion assembly, and enhances the transcription efficiency of the virus (55, 56). It contains three highly conserved and distinct domains, namely, an NTD, an RNA-binding domain or a linker region (LKR), and a CTD (57). The NTD binds with the 3′ end of the viral genome, perhaps via electrostatic interactions, and is highly diverged both in length and sequence (58). The charged LKR is serine and arginine rich and is also known as the SR (serine and arginine) domain (59). The LKR is capable of direct interaction with in vitro RNA interaction and is responsible for cell signaling (60, 61). It also modulates the antiviral response of the host by working as an antagonist for interferon

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article gives a bird's eye view about this new virus. Since knowledge about this virus is rapidly evolving, readers are urged to update themselves regularly.

History

Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name coronavirus [3]. Four corona viruses namely HKU1, NL63, 229E and OC43 have been in circulation in humans, and generally cause mild respiratory disease.

There have been two events in the past two decades wherein crossover of animal betacorona viruses to humans has resulted in severe disease. The first such instance was in 2002–2003 when a

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been controlled by adopting appropriate and strict prevention and control measures, and patients for clinical trials will not be available. The newly developed drugs cannot be marketed due to the lack of end users.

Vaccines
The S protein plays a significant role in the induction of protective immunity against SARS-CoV by mediating T-cell responses and neutralizing antibody production (168). In the past few decades, we have seen several attempts to develop a vaccine against human coronaviruses by using S protein as the target (168, 169). However, the developed vaccines have minimal application, even among closely related strains of the virus, due to a lack of cross-protection. That is mainly because of the extensive diversity existing among the different antigenic variants of the virus (104). The contributions of the structural proteins, like spike (S), matrix (M), small envelope (E), and nucleocapsid (N) proteins, of SARS-CoV to induce protective immunity has been evaluated by expressing them in a recombinant parainfluenza virus type 3 vector (BHPIV3). Of note, the result was conclusive that the expression of M, E, or N proteins without the presence of S protein would not

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samples obtained from lower respiratory tracts. Hence, based on the viral load, we can quickly evaluate the progression of infection (291). In addition to all of the above findings, sequencing and phylogenetics are critical in the correct identification and confirmation of the causative viral agent and useful to establish relationships with previous isolates and sequences, as well as to know, especially during an epidemic, the nucleotide and amino acid mutations and the molecular divergence. The rapid development and implementation of diagnostic tests against emerging novel diseases like COVID-19 pose significant challenges due to the lack of resources and logistical limitations associated with an outbreak (155).

SARS-CoV-2 infection can also be confirmed by isolation and culturing. The human airway epithelial cell culture was found to be useful in isolating SARS-CoV-2 (3). The efficient control of an outbreak depends on the rapid diagnosis of the disease. Recently, in response to the COVID-19 outbreak, 1-step quantitative real-time reverse transcription-PCR assays were developed that detect the ORF1b and N regions of the SARS-CoV-2 genome (156). That assay was found to achieve the rapid detection of SARS-CoV-2. Nucleic acid-based assays offer high accuracy in the diagnosis of SARS-

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cat and camels, respectively, act as amplifier hosts (40, 41).

Coronaviruses genomes and subgenomes encode six ORFs (31). The majority of the 5′ end is occupied by ORF1a/b, which produces 16 nsps. The two polyproteins, pp1a and pp1ab, are initially produced from ORF1a/b by a −1 frameshift between ORF1a and ORF1b (32). The virus-encoded proteases cleave polyproteins into individual nsps (main protease [Mpro], chymotrypsin-like protease [3CLpro], and papain-like proteases [PLPs]) (42). SARS-CoV-2 also encodes these nsps, and their functions have been elucidated recently (31). Remarkably, a difference between SARS-CoV-2 and other CoVs is the identification of a novel short putative protein within the ORF3 band, a secreted protein with an alpha helix and beta-sheet with six strands encoded by ORF8 (31).

Coronaviruses encode four major structural proteins, namely, spike (S), membrane (M), envelope (E), and nucleocapsid (N), which are described in detail below.

S Glycoprotein
Coronavirus S protein is a large, multifunctional class I viral transmembrane protein. The size of this

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The interferon response is one of the major innate immunity defences against virus invasion. Interferons induce the expression of diverse interferon-stimulated genes, which can interfere with every step of virus replication. Previous studies identified type I interferons as a promising therapeutic candidate for SARS[149]. In vitro data showed SARS-CoV-2 is even more sensitive to type I interferons than SARS-CoV, suggesting the potential effectiveness of type I interferons in the early treatment of COVID-19 (REF.[150]). In China, vapor inhalation of interferon-α is included in the COVID-19 treatment guideline[151]. Clinical trials are ongoing across the world to evaluate the efficacy of different therapies involving interferons, either alone or in combination with other agents[152].

Immunoglobulin therapy.
Convalescent plasma treatment is another potential adjunctive therapy for COVID-19. Preliminary findings have suggested improved clinical status after the treatment[153],[154]. The FDA has provided guidance for the use of COVID-19 convalescent plasma under an emergency investigational new drug application. However, this treatment may have adverse effects by causing antibody-mediated enhancement of infection, transfusion-associated acute lung injury and allergic transfusion reactions.

Monoclonal antibody therapy is an effective immunotherapy for the treatment of some viral infections in recent patients. Recent studies reported specific monoclonal antibodies neutralizing SARS-CoV-2 infection

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or even die, whereas most young people and children have only mild diseases (non-pneumonia or mild pneumonia) or are asymptomatic[9,81,82]. Notably, the risk of disease was not higher for pregnant women. However, evidence of transplacental transmission of SARS-CoV-2 from an infected mother to a neonate was reported, although it was an isolated case[83,84]. On infection, the most common symptoms are fever, fatigue and dry cough[13.60,80,81]. Less common symptoms include sputum production, headache, haemoptysis, diarrhoea, anorexia, sore throat, chest pain, chills and nausea and vomiting in studies of patients in China[13.60,80,81]. Self-reported olfactory and taste disorders were also reported by patients in Italy[85]. Most people showed signs of diseases after an incubation period of 1–14 days (most commonly around 5 days), and dyspnoea and pneumonia developed within a median time of 8 days from illness onset[9].

In a report of 72,314 cases in China, 81% of the cases were classified as mild, 14% were severe cases that required ventilation in an intensive care unit (ICU) and a 5% were critical (that is, the patients had respiratory failure, septic shock and/or multiple organ dysfunction or failure)[9,86]. On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT)[13.60,80,81]. Most patients also developed marked lymphopenia, similar to what had been seen in patients with SARS and MERS, and non-survivors developed more severe lymphopenia over time[13.60,80,81]. Compared with non-ICU patients had higher levels

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require sedatives, analgesics, and even muscle relaxation drugs to prevent ventilator-related lung injury associated with human-machine incoordination (122). The result obtained from a clinical study of four patients infected with COVID-19 claimed that combination therapy using lopinavir/ritonavir, arbidol, and Shufeng Jiedu capsules (traditional Chinese medicine) was found to be effective in managing COVID-19 pneumonia (193). It is difficult to evaluate the therapeutic potential of a drug or a combination of drugs for managing a disease based on such a limited sample size. Before choosing the ideal therapeutic agent for the management of COVID-19, randomized clinical control studies should be performed with a sufficient study population.

Antiviral Drugs

Several classes of routinely used antiviral drugs, like oseltamivir (neuraminidase inhibitor), acyclovir, ganciclovir, and ribavirin, do not have any effect on COVID-19 and, hence, are not recommended (187). Oseltamivir, a neuraminidase inhibitor, has been explored in Chinese hospitals for treating suspected COVID-19 cases, although proven efficacy against SARS-CoV-2 is still lacking for this drug (7). The in vitro antiviral potential of FAD-approved drugs, viz.,

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Cases continued to increase exponentially and modelling studies reported an epidemic doubling time of 1.8 d [10]. In fact on the 12th of February, China changed its definition of confirmed cases to include patients with negative/ pending molecular tests but with clinical, radiologic and epidemiologic features of COVID-19 leading to an increase in cases by 15,000 in a single day [6]. As of 05/03/2020 96,000 cases worldwide (80,000 in China) and 87 other countries and 1 international conveyance (696, in the cruise ship Diamond Princess parked off the coast of Japan) have been reported [2]. It is important to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition,