

0101

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 at least 3 d and have two consecutive negative molecular tests at 1 d sampling interval. This recommendation is different from pandemic flu where patients were

0102

- All clinicians should keep themselves updated about recent developments including global spread of the disease.
- Non-essential international travel should be avoided at this time.
- People should stop spreading myths and false information about the disease and try to allay panic and anxiety of the public.

Conclusions

This new virus outbreak has challenged the economic, medical and public health infrastructure of China and to some extent, of other countries especially, its neighbours. Time alone will tell how the virus will impact our lives here in India. More so, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. Therefore, apart from curbing this outbreak, efforts should be made to

considerable protection in mice against a MERS-CoV lethal challenge. Such antibodies may play a crucial role in enhancing protective humoral responses against the emerging CoVs by aiming appropriate epitopes and functions of the S protein. The cross-neutralization ability of SARS-CoV RBD-specific neutralizing MAbs considerably relies on the resemblance between their RBDs; therefore, SARS-CoV RBD-specific antibodies could cross-neutralized SL CoVs, i.e., bat-SL-CoV strain WIV1(RBD with eight amino acid differences from SARS-CoV) but not bat-SL-CoV strain SHC014 (24 amino acid differences) (200).

Appropriate RBD-specific MAbs can be recognized by a relative analysis of RBD of SARS-CoV-2 to that of SARS-CoV, and cross-neutralizing SARS-CoV RBD-specific MAbs could be explored for their effectiveness against COVID-19 and further need to be assessed clinically. The U.S. biotechnology company Regeneron is attempting to recognize potent and specific MAbs to combat COVID-19. An ideal therapeutic option suggested for SARS-CoV-2 (COVID-19) is the combination therapy comprised of MAbs and the drug remdesivir (COVID-19) (201). The SARS-CoV-specific human Mab CR3022 is found to bind with SARS-CoV-2 RBD, indicating its potential as a therapeutic agent

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

other clinical trials in different phases are still ongoing elsewhere.

Immunomodulatory agents. SARS-CoV-2 triggers a strong immune response which may cause cytokine storm syndrome^{60,61}. Thus, immunomodulatory agents that inhibit the excessive inflammatory response may be a potential adjunctive therapy for COVID-19. Dexamethasone is a corticosteroid often used in a wide range of conditions to relieve inflammation through its anti-inflammatory and immunosuppressant effects. Recently, the RECOVERY trial found dexamethasone reduced mortality by about one third in hospitalized patients with COVID-19 who received invasive mechanical ventilation and by one fifth in patients receiving oxygen. By contrast, no benefit was found in patients without respiratory support¹⁴⁶.

Tocilizumab and sarilumab, two types of interleukin-6 (IL-6) receptor-specific antibodies previously used to treat various types of arthritis, including rheumatoid arthritis, and cytokine release syndrome, showed effectiveness in the treatment of severe COVID-19 by attenuating the cytokine storm in a small uncontrolled trial¹⁴⁷. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) medication that could potentially reduce pulmonary oedema in patients with severe COVID-19. Eculizumab is a specific monoclonal antibody that inhibits the proinflammatory complement protein C5. Preliminary results showed that it induced a drop of inflammatory markers and C-reactive protein levels, suggesting its potential to be an option for the treatment of severe COVID-19 (REF.¹⁴⁸).

another study, the average reproductive number of COVID-19 was found to be a 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

0127

been used based on the experience with SARS and MERS. In a historical control study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone [15].

In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4%, extracorporeal membrane oxygenation (ECMO) in 3%, continuous renal replacement therapy (CRRT) in 9%, antibiotics in 71%, antifungals in 15% glucocorticoids in 19% and intravenous immunoglobulin therapy in 27% [15]. Antiviral therapy consisting of oseltamivir, ganciclovir and lopinavir-ritonavir was given to 75% of the patients. The duration of non-invasive ventilation was 4-22 d [median 9 d]

had >95% homology with the bat coronavirus and >70% similarity with the SARS-CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there [7]. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [8]. The first fatal case was reported on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th Jan, 2020. By 23rd January, the 11 million population of Wuhan was placed under lock down

extended to other cities or Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [9]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travellers returning from China, placed all people symptomatic or otherwise in isolation for 14 d and tested them for the virus.

Cases continued to increase exponentially and modelling studies

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

13 CONVALESCENT PLASMA THERAPY

Guo Yanhong, an official with the National Health Commission (NHV), stated that convalescent plasma therapy is a significant method for treating severe COVID-19 patients.

Among the COVID-19 patients currently receiving convalescent plasma therapy in the virus-hit Wuhan, one has been discharged from hospital, as reported by Chinese science authorities on Monday, 17th February 2020 in Beijing. The first dose of convalescent plasma from a COVID-19 patient was collected on 1st and 9th February 2020 from a severely ill patient who was given treatment at a hospital in Jiangxia District in Wuhan. The presence of the virus in patients is minimized by the antibodies in the convalescent plasma. Guiqiang stated that donating plasma may cause minimal harm to the donor and that there is nothing to be worried about. Plasma donors must be cured patients and discharged from hospital. Only plasma is used, whereas red blood cells (RBC), white blood cells (WBC) and blood platelets are transfused back into the donor's body. Wang alleged that donor's plasma will totally improve to its initial state after one or 2 weeks from the day of plasma donation of around 200 to 300 millilitres.⁶¹

0148

Epidemiology and Pathogenesis [10, 11]

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms [9]. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [12]. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK [6]. These infected droplets can spread 1-2 m and deposit

0155

Prevention [21, 30]

Since at this time there are no approved treatments for this infection, prevention is crucial. Several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery.

Isolation of confirmed or suspected cases with mild illness at home is recommended. The ventilation at home should be good with sunlight to allow for destruction of virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene.

absence of this protein is related to the altered virulence of coronavirus 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

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 on the experience with SARS and MERS. In a historical

(173, 174). Hence, knowledge and understanding of S protein-based vaccine development in SARS-CoV will help to identify potential S protein vaccine candidates in SARS-CoV-2. Therefore, vaccine strategies based on the whole S protein, S protein subunits, or specific potential epitopes of S protein appear to be the most promising vaccine candidates against coronaviruses. The RBD of the S1 subunit of S protein has a superior capacity to induce neutralizing antibodies. This property of the RBD can be utilized for designing potential SARS-CoV vaccines either by using RBD-containing recombinant proteins or recombinant vectors that encode RBD (175). Hence, the superior genetic similarity existing between SARS-CoV-2 and SARS-CoV can be utilized to repurpose vaccines that have proven *in vitro* efficacy against SARS-CoV to be utilized for SARS-CoV-2. The possibility of cross-protection in COVID-19 was evaluated by comparing the S protein sequences of SARS-CoV-2 with that of SARS-CoV. The comparative analysis confirmed that the variable residues were found concentrated on the S1 subunit of S protein, an important vaccine target of the virus (150). Hence, the possibility of SARS-CoV-specific neutralizing antibodies providing cross-protection to COVID-19 might be lower. Further genetic analysis is required

0172

including IL2, IL10, GCSF, IP10, MCP1, MIP1A, and TNF α [15]. The median time from onset of symptoms to dyspnea was 5 d, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8 d. the need for intensive care admission was in 25-30% of affected patients in published series. Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd wk. the median duration of hospital stay in those who recovered was 10 d. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50-75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3% [2].

Interestingly, disease in patients outside Hubei province has been

system (30).

Bovine coronaviruses (BoCoVs) are known to infect several domestic and wild ruminants (126). BoCoV inflicts neonatal calf diarrhea in adult cattle, leading to bloody diarrhea (winter dysentery) and respiratory disease complex (shipping fever) in cattle of all age groups (126). BoCoV-like viruses have been noted in humans, suggesting its zoonotic potential as well (127). Feline enteric and feline infectious peritonitis (FIP) viruses are the two major feline CoVs (128), where feline CoVs can affect the gastrointestinal tract, abdominal cavity (peritonitis), respiratory tract, and central nervous system (128). Canines are also affected by CoVs that fall under different genera, namely, canine enteric coronavirus in *Alphacoronavirus* and canine respiratory coronavirus in *Betacoronavirus*, affecting the enteric and respiratory tract, respectively (129, 130). IBV, under *Gammacoronavirus*, causes diseases of respiratory, urinary, and reproductive systems, with substantial economic losses in chickens (131, 132). In small laboratory animals, mouse hepatitis virus, rat sialodacryoadenitis coronavirus, and guinea pig and rabbit coronaviruses are the major CoVs associated with disease manifestation like enteritis, hepatitis, and respiratory infections (10,133)

Swine acute diarrhea syndrome coronavirus

This emerging virus will establish a niche in humans and coexist with us for a long time¹⁶⁶. Before clinically approved vaccines are widely available, there is no better way to protect us from SARS-CoV-2 than personal preventive behaviours such as social distancing and wearing masks, and public health measures, including active testing, case tracing and restrictions on social gatherings. Despite a flood of SARS-CoV-2 research published every week, current knowledge of this novel coronavirus is just the tip of the iceberg. The animal origin and cross-species infection route of SARS-CoV-2 are yet to be uncovered. The molecular mechanisms of SARS-CoV-2 infection pathogenesis and virus-host

droplets can spread 1-2 m and deposit on surfaces. The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [13]. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them and then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized [6]. As per current information, transplacental transmission from pregnant women to their fetus has not been described [14]. However, neonatal disease due to postnatal transmission is described [14]. The incubation period varies from 2 to 14 d [median 5 d]. Studies have identified angiotensin receptor 2

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 ACE₂ 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

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

only a matter of time before another zoonotic coronavirus results in an epidemic by jumping the so-called species barrier (287).

The host spectrum of coronavirus increased when a novel coronavirus, namely SW1, was recognized in the liver tissue of a captive beluga whale (*Delphinapterus leucas*) (138). In recent decades, several novel coronaviruses were identified from different animal species. Bats can harbor these viruses without manifesting any clinical disease but are persistently infected (30). They are the only mammals with the capacity for self-powered flight, which enables them to migrate long distances, unlike land mammals. Bats are distributed worldwide and also account for about a fifth of all mammalian species (6). This makes them the ideal reservoir host for many viral agents and also the source of novel coronaviruses that have yet to be identified. It has become a necessity to study the diversity of coronavirus in the bat population to prevent future outbreaks that could jeopardize livestock and public health. The repeated outbreaks caused by bat-origin coronaviruses calls for the development of efficient molecular surveillance strategies for studying *Betacoronavirus* among animals (12), especially in the *Rhinolophus* bat family (86). Chinese bats have high commercial value, since they are used in

comprised a small population and, hence, the possibility of misinterpretation could arise. However, in another case study, the authors raised concerns over the efficacy of hydroxychloroquine-azithromycin in the treatment of COVID-19 patients, since no observable effect was seen when they were used. In some cases, the treatment was discontinued due to the prolongation of the QT interval (307). Hence, further randomized clinical trials are required before concluding this matter.

Recently, another FDA-approved drug, ivermectin, was reported to inhibit the *in vitro* replication of SARS-CoV-2. The findings from this study indicate that a single treatment of this drug was able to induce an ~5,000-fold reduction in the viral RNA at 48 h in cell culture. (308). One of the main disadvantages that limit the clinical utility of ivermectin is its potential to cause cytotoxicity. However, altering the vehicles used in the formulations, the pharmacokinetic properties can be modified, thereby having significant control over the systemic concentration of ivermectin (338). Based on the pharmacokinetic simulation, it was also found that ivermectin may have limited therapeutic utility in managing COVID-19, since the inhibitory concentration that has to be achieved for effective anti-SARS-CoV-2 activity is far higher than the

SARS- or MERS-CoV outbreak (120). However, there has been concern regarding the impact of SARS-CoV-2/COVID-19 on pregnancy. Researchers have mentioned the probability of *in utero* transmission of novel SARS-CoV-2 from COVID-19-infected mothers to their neonates in China based upon the rise in IgM and IgG antibody levels and cytokine values in the blood obtained from newborn infants immediately postbirth; however, RT-PCR failed to confirm the presence of SARS-CoV-2 genetic material in the infants (283). Recent studies show that at least in some cases, preterm delivery and its consequences are associated with the virus. Nonetheless, some cases have raised doubts for the likelihood of vertical transmission (240-243).

COVID-19 infection was associated with pneumonia, and some developed acute respiratory distress syndrome (ARDS). The blood biochemistry indexes, such as albumin, lactate dehydrogenase, C-reactive protein, lymphocytes (percent), and neutrophils (percent) give an idea about the disease severity in COVID-19, patients may present leukocytosis, leukopenia with lymphopenia (244), hypoalbuminemia, and an increase of lactate dehydrogenase, aspartate transaminase, alanine aminotransferase, bilirubin, and, especially, D-dimer

0194

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

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 Italy⁸⁵. 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 onset⁹.

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 was observed in patients with SARS and MERS, and non-survivors developed severer lymphopenia over time^{13,60,80,81}. Compared with non-ICU patients had higher levels

0196

of persistent local transmission or contact with patients with similar travel history or those with confirmed COVID-19 infection. However cases may be asymptomatic or even without fever. A confirmed case is a suspect case with a positive molecular test.

Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stool and in severe cases, the blood. It must be remembered that the multiplex PCR panels currently available do not include the COVID-19. Commercial tests are also not available at present. In a suspect case in India, the appropriate sample has to be sent to designated reference labs in India or the National Institute of Virology in Pune. As the epidemic progresses, commercial tests

in Yunnan. This novel bat virus, denoted 'RmYN02', is 93.3% identical to SARS-CoV-2 across the genome. In the long *lab* gene, it exhibits 97.2% identity to SARS-CoV-2, which is even higher than for a RaTG13 (REF.²⁸). In addition to RaTG13 and RmYN02, phylogenetic analysis shows that bat coronavirus ZC45 and ZXC21 previously detected in *Rhinolophus pusillus* bats from eastern China also fall into the SARS-CoV-2 lineage of the subgenus Sarbecovirus³⁶ (FIG. 2). The discovery of diverse bat coronavirus closely related to SARS-CoV-2 suggests that bats are possible reservoirs of SARS-CoV-2 (REF.³⁷). Nevertheless, on the basis of current findings, the divergence between SARS-CoV-2 and related bat coronaviruses likely represent more than 20 years of sequence evolution, suggesting that these bat coronaviruses can be regarded only as the likely evolutionary precursor of SARS-CoV-2 but not as the direct progenitor of SARS-CoV-2 (REF.³⁸).

Beyond bats, pangolins are another wildlife host probably linked with SARS-CoV-2. Multiple SARS-CoV-2-related viruses have been identified in tissues of Malayan pangolins smuggled from Southeast Asia into southern China from 2017 to 2019. These viruses from pangolins independently seized by Guangxi and Guangdong provincial customs belong to two distinct sublineages³⁹⁻⁴¹. The Guangdong strains, which were isolated or sequenced by different research groups from smuggled pangolins, have 99.8% sequence identity with each other⁴¹. They are very closely related to SARS-CoV-2, exhibiting 92.4% sequence similarity. Notably, the RBD of Guangdong pangolin coronaviruses is highly similar to that of SARS-CoV-2. The receptor-binding motif (RBM; which is part of the RBD) of these viruses has only one amino acid variation from SARS-CoV-2, and it is identical to that of SARS-CoV-2 in all five critical

0202

identified angiotensin receptor 2 (ACE₂) as the receptor through which the virus enters the respiratory mucosa [11].

The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies [11]. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009 [2].

Clinical Features [8, 15-18]

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical features include fever (not in all), cough sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from

recovered patients and used for plasma transfusion twice in a volume of 200 to 250 ml on the day of collection (310). At present, treatment for sepsis and ARDS mainly involves antimicrobial therapy, source control, and supportive care. Hence, the use of therapeutic plasma exchange can be considered an option in managing such severe conditions. Further randomized trials can be designed to investigate its efficacy (311).

Potential Therapeutic Agents

Potent therapeutics to combat SARS-CoV-2 infection include virus binding molecules, molecules or inhibitors targeting particular enzymes implicated in replication and transcription process of the virus, helicase inhibitors, short interfering RNA (siRNA), neutralizing antibodies, MAbs against the host receptor, MAbs interfering with the S1 RBD, antiviral peptide aimed at S2, and natural drugs/medicines (7, 166, 186). The S protein acts as the critical target for developing CoV antivirals, like inhibitors of S protein and S cleavage, neutralizing antibodies, RBD-ACE2 blockers, siRNAs, blockers of the fusion core, and proteases (168).

All of these therapeutic approaches have revealed

0209

Origin and Spread of COVID-19 [1, 2, 6]

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat

0212

infections clinically or through routine lab tests. Therefore travel history becomes important. However, as the epidemic spreads, the travel history will become irrelevant.

Treatment [21, 23]

Treatment is essentially supportive and symptomatic.

The first step is to ensure adequate isolation (discussed later) to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Routine use of antibiotics and antivirals such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal

with COVID-19 showed typical features on initial CT, including bilateral multilobar ground-glass opacities with a peripheral or posterior distribution^{118,119}. Thus, it has been suggested that CT scanning combined with repeated swab tests should be used for individuals with high clinical suspicion of COVID-19 but who test negative in initial nucleic acid screening¹¹⁸. Finally, SARS-CoV-2 serological tests detecting antibodies to N or S protein could complement molecular diagnosis, particularly in late phases after disease onset or for retrospective studies^{116,120,121}. However, the extent and duration of immune responses are still unclear, and available serological tests differ in their sensitivity and specificity, all of which need to be taken into account when one is deciding on serological tests and interpreting their results or potentially in the future test for T cell responses.

Therapeutics

To date, there are no generally proven effective therapies for COVID-19 or antivirals against SARS-CoV-2, although some treatments have shown some benefits in certain subpopulations of patients or for certain end points (see later). Researchers and manufacturers are conducting large-scale clinical trials to evaluate various therapies for COVID-19. As of 2 October 2020, there were about 405 therapeutic drugs in development for COVID-19, and nearly 318 in human clinical trials ([COVID-19 vaccine and therapeutic tracker](#)). In the following sections, we summarize potential therapeutics against SARS-CoV-2 on the basis of published clinical data and experience.

0218

comorbidities), it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. The case fatality rate is estimated to range from 2 to 3%. Diagnosis is by demonstration of the virus in respiratory secretions by special molecular tests. Common laboratory findings include normal/low white cell counts with elevated c-reactive protein (CRP). The computerized tomographic chest scan is usually abnormal even in those with no symptoms or mild disease. Treatment is essentially supportive; role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors the SARS-CoV

0225

epidemic progresses, commercial tests will become available.

Other laboratory investigations are usually non specific. The white cell count is usually normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated but procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH may be elevated and high levels are associated with severe disease.

The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease. The CT is more sensitive and specific. CT imaging generally shows infiltrates, ground glass opacities and sub segmental

and chest discomfort, and in severe cases dyspnea and bilateral lung infiltration^{6,7}. Among the first 27 documented hospitalized patients, most cases were epidemiologically linked to Huanan Seafood Wholesale Market, a wet market located in downtown Wuhan, which sells not only seafood but also live animals, including poultry and wildlife^{4,8}. According to retrospective study, the onset of the first known case dates back to 8 December 2019 (REF⁹). On 31 December, Wuhan Municipal Health Commission notified the public of a pneumonia outbreak of unidentified cause and informed the World Health Organization (WHO)⁹ (FIG. 1).

By metagenomic RNA sequencing and virus isolation from bronchoalveolar lavage fluid samples from patients with severe pneumonia, independent teams of Chinese scientists identified that the causative agent of this emerging disease is a betacoronavirus that had never been seen before^{6,10,11}. On 9 January 2020, the result of this etiological identification was publicly announced (FIG. 1). The first genome sequence of the novel coronavirus was published on the Virological website on 10 January, and more nearly complete genome sequences determined by different research institutes were then released via the GISAID database on 12 January⁷. Later, more patients with no history of exposure to Huanan Seafood Wholesale Market were identified. Several familial clusters of infection were reported and nosocomial infection also occurred in health-care facilities. All these cases provided clear evidence for human-to-human transmission of the new virus^{4,12-14}. As the outbreak coincided with the approach of the lunar New Year, travel between cities before the festival facilitated virus transmission in China. This novel coronavirus pneumonia soon spread to other cities in Hubei province and to other parts of China. Within 1 month

0228

such instance was in 2002-2003 when a new coronavirus of the β genera and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, designated as severe acute respiratory syndrome coronavirus affected 8422 people mostly in China and Hongkong and caused 916 deaths (mortality rate 11%) before being contained [4]. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%) [5].

Origin and Spread of COVID-19 [1, 2, 6]

In December 2019, adults in Wuhan, capital city of Hubei province and a

0230

[median 17 d]. in the case series of children discussed earlier, all children recovered with basic treatment and did not need intensive care [17].

There is anecdotal experience with use of remdesvir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19 [27]. More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19 [21, 28, 29]. Additionally, recommendations about using traditional Chinese herbs find place in the Chinese guidelines [21].

Prevention [21, 30]

0233

exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [2]. India, which had reported only 3 cases till 2/3/3030, has also seen a sudden spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined.

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary

lower respiratory tracts. Acute viral interstitial pneumonia and humoral and cellular immune responses were observed^{48,75}. Moreover, prolonged virus shedding peaked early in the course of infection in asymptomatic macaques⁶⁹, and old monkeys showed severer interstitial pneumonia than young monkeys⁷⁶, which is similar to what is seen in patients with COVID-19. In human *ACE2*-transgenic mice infected with SARS-CoV-2, typical interstitial pneumonia was present, and viral antigens were observed mainly in the bronchial epithelial cells, macrophages and alveolar epithelia. Some human *ACE2*-transgenic mice even died after infection^{70,71}. In wide-type mice, a SARS-CoV-2 mouse-adapted strain with the N501Y alteration in the RBD of the S protein was generated at passage 6. Interstitial pneumonia and inflammatory responses were found in both young and aged mice after infection with the mouse-adapted strain⁷⁴. Golden hamsters also showed typical symptoms after being infected with SARS-CoV-2 [REF.⁷⁷]. In other animal models, including cats and ferrets, SARS-CoV-2 could efficiently replicate in the upper respiratory tract but did not induce severe clinical symptoms^{43,78}. As transmission by direct contact and air was observed in infected ferrets and hamsters, these animals could be used to model different transmission modes of COVID-19 [REFS⁷⁷⁻⁷⁹]. Animal models offer important information for understanding the pathogenesis of SARS-CoV-2 infection and the transmission dynamics of SARS-CoV-2, and are important to evaluate the efficacy of antiviral therapeutics and vaccines.

Clinical and epidemiological features

It appears that all ages of the population are susceptible to SARS-CoV-2, and the median age of infection is around 50 years^{9,13,60,80,81}. However, clinical manifestations differ with age. In general, older men (>60 years old) with co-morbidities are more likely to develop severe respiratory disease that requires hospitalization

0237

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 betacoronavirus to humans has resulted in severe disease. The first such instance was in 2002-2003 when a

0238

(entertainment parks etc). China is also considering introducing legislation to prohibit selling and trading of wild animals [32].

The international response has been dramatic. Initially, there were massive travel restrictions to China and people returning from China/ evacuated from China are being evaluated for clinical symptoms, isolated and tested for COVID-19 for 2 wks even if asymptomatic. However, now with rapid world wide spread of the virus these travel restrictions have extended to other countries. Whether these efforts will lead to slowing of viral spread is not known.

A candidate vaccine is under development.

Practice Points from an Indian Perspective

0245

pandemic flu where patients were asked to resume work/school once afebrile for 24 h or by day 7 of illness. Negative molecular tests were not a prerequisite for discharge.

At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene frequently every 15-20 min. Patients with respiratory symptoms should be asked to use surgical masks. The use of mask by health people in public places has not shown to protect against respiratory viral infections and is currently not recommended by WHO. However, in China, the public has been asked to wear masks in public and especially in crowded places and large scale gatherings are prohibited (entertainment parks etc). China is also

risk regions. It is derived from a live attenuated strain of *Mycobacterium bovis*. At present, three new clinical trials have been registered to evaluate the protective role of BCG vaccination against SARS-CoV-2 (363). Recently, a cohort study was conducted to evaluate the impact of childhood BCG vaccination in COVID-19 PCR positivity rates. However, childhood BCG vaccination was found to be associated with a rate of COVID-19-positive test results similar to that of the nonvaccinated group (364). Further studies are required to analyze whether BCG vaccination in childhood can induce protective effects against COVID-19 in adulthood. Population genetic studies conducted on 103 genomes identified that the SARS-CoV-2 virus has evolved into two major types, L and S. Among the two types, L type is expected to be the most prevalent (~70%), followed by the S type (~30%) (366). This finding has a significant impact on our race to develop an ideal vaccine, since the vaccine candidate has to target both strains to be considered effective. At present, the genetic differences between the L and S types are very small and may not affect the immune response. However, we can expect further genetic variations in the coming days that could lead to the emergence of new strains (367).

0250

mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15-20 min.

The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers [31]. Till date, almost 1500 healthcare workers in China have been infected with 6 deaths. The doctor who first warned about the virus has died too. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for

0252

exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [2]. India, which had reported only 3 cases till 2/3/3030, has also seen a sudden spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined.

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary

SplitsTree phylogeny analysis.

In the unrooted phylogenetic tree of different betacoronavirus based on the S protein, virus sequences from different subgenera grouped into separate clusters. SARS-CoV-2 sequences from Wuhan and other countries exhibited a close relationship and appeared in a single cluster (Fig. 1). The CoVs from the subgenus *Sarbecovirus* appeared jointly in SplitsTree and divided into three subclusters, namely, SARS-CoV-2, bat- SARS-like-CoV (bat-SL-CoV), and SARS-CoV (Fig. 1). In the case of other subgenera, like *Merbecovirus*, all of the sequences grouped in a single cluster, whereas in *Embecovirus*, different species, comprised of canine respiratory CoVs, bovine CoVs, equine CoVs, and human CoV strain (OC43), grouped in a common cluster. Isolates in the subgenera *Nobecovorus* and *Hibecovirus* were found to be places separately away from other reported SARS-CoVs but shared a bat origin.

CURRENT WORLDWIDE SCENARIO OF SARS-CoV-2

This novel virus, SARS-CoV-2, comes under the subgenus *Sarbecovirus* of the *Osthocoronavirinae* subfamily and is entirely different from the viruses

other emerging viral diseases. Several therapeutic and preventive strategies, including vaccines, immunotherapeutics, and antiviral drugs, have been exploited against the previous CoV outbreaks (SARS-CoV and MERS-CoV) (8, 104, 164-167). These valuable options have already been evaluated for their potency, efficacy, and safety, along with several other types of current research that will fuel our search for ideal therapeutic agents against COVID-19 (7, 9, 19, 21, 36). The primary cause of the unavailability of approved and commercial vaccines, drugs, and therapeutics to counter the earlier SARS-CoV-2 and MERS-CoV seems to owe to the lesser attention of the biomedicine and pharmaceutical companies, as these two CoVs did not cause much havoc, global threat, and panic like those posed by the SARS-CoV-2 pandemic (19). Moreover, for such outbreak situations, the requirement for vaccines and therapeutic/drugs exists only for a limited period, until the outbreak is controlled. The proportion of the human population infected with SARS-CoV and MERS-CoV was also much lower across the globe, failing to attract drug and vaccine manufacturers and producers. Therefore, by the time an effective drug or vaccine is designed against such disease outbreaks, the virus would have been controlled by adopting appropriate and strict

Practice Points from an Indian Perspective

At the time of writing this article, the risk of coronavirus in India is extremely low. But that may change in the next few weeks. Hence the following is recommended:

- Healthcare providers should take travel history of all patients with respiratory symptoms, and any international travel in the past 2 wks as well as contact with sick people who have travelled internationally.
- They should set up a system of system of triage of patients with respiratory illness in the outpatient department and give them a simple surgical mask to wear. They should use surgical masks themselves while examining such