upward to be revenged upon Tarzan, but the ape man was otherwise engaged and did not wish to be interrupted. He was explaining again to Taug the depths of the latter's abysmal ignorance, and pointing out how much greater and mightier was Tarzan of the Apes than Taug or any other ape.

In the end he would release Taug, but not until Taug was fully acquainted with his own inferiority. And then the maddened bull came from beneath, and instantly Tarzan was transformed from a good-natured, teasing youth into a snarling, savage beast. Along his scalp the hair bristled: his upper lip drew back that his fighting fangs might be uncovered and ready. He did not wait for the bull to reach him, for something in the appearance or the voice of the attacker aroused within the ape-man a feeling of belligerent antagonism that would not be denied. With a scream that carried no human note, Tarzan leaped straight at the throat of the attacker.

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whiplike motion; but realizing from past experience the futility of long distance argument with the ape-man, he turned presently and struck off into the tangled vegetation which hid him from the view of his tormentor. With a final scream of jungle invective and an apelike grimace at his departing foe, Tarzan continued along his way.

Another mile and a shifting wind brought to his keen nostrils a familiar, pungent odor close at hand, and a moment later there loomed beneath him a huge, gray-black bulk forging steadily along the jungle trail. Tarzan seized and broke a small tree limb, and at the sudden cracking sound the ponderous figure halted. Great ears were thrown forward, and a long, supple trunk rose quickly to wave to and fro in search of the scent of an enemy, while two weak, little eyes peered suspiciously and futilely about in quest of the author of the noise which had disturbed his peaceful way.

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scarce daring to breathe, and then, very faintly but unmistakable to her keen ears, came the stealthy crunching of twigs and grasses beneath padded feet.

All about Momaya grew the giant trees of the tropical jungle, festooned with hanging vines and mosses. She seized upon the nearest and started to clamber, apelike, to the branches above. As she did so, there was a sudden rush of a great body behind her, a menacing roar that caused the earth to tremble, and something crashed into the very creepers to which she was clinging--but below her.

Momaya drew herself to safety among the leafy branches and thanked the foresight which had prompted her to bring along the dried human ear which hung from a cord about her neck. She always had known that that ear was good medicine. It had been given her, when a girl, by the witch-doctor of her town tribe, and

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Tarzan sighed. His newly acquired balu had much indeed to learn. It was pitiful that a balu of his size and strength should be so backward. He tried to coax Tibo to follow him; but the child dared not, so Tarzan picked him up and carried him upon his back. Tibo no longer scratched or bit. Escape seemed impossible. Even now, were he set upon the ground, the chance was remote, he knew, that he could find his way back to the village of Mbonga, the chief. Even if he could, there were the lions and the leopards and the hyenas, any one of which, as Tibo was well aware, was particularly fond of the meat of little black boys.

So far the terrible white god of the jungle had offered him no harm. He could not expect even this much consideration from the frightful, green-eyed man-eaters. It would be the lesser of two evils, then, to let the white god carry him away without scratching and biting, as he had done at first.

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"Tell me," he continued, "if you be the great king who sends Ara, the lightning; who makes the great noise and the mighty winds, and sends the waters down upon the jungle people when the days are dark and it is cold. Tell me, Goro, are you God?"

Of course he did not pronounce God as you or I would pronounce His name, for Tarzan knew naught of the spoken language of his English forbears; but he had a name of his own invention for each of the little bugs which constituted the alphabet. Unlike the apes he was not satisfied merely to have a mental picture of the things he knew, he must have a word descriptive of each. In reading he grasped a word in its entirety; but when he spoke the words he had learned from the books of his father, he pronounced each according to the names he had given the various little bugs which occurred in it, usually giving the gender prefix for each.

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quick glance into the tree whose safety she had gained not an instant too soon, and Sheeta was charging. It was useless to risk his life in idle and unequal combat from which no good could come; but could he escape a battle with the enraged cat? And if he was forced to fight, what chance had he to survive? Tarzan constrained to admit that his position was aught but a desirable one. The trees were too far to hope to reach in time to elude the cat. Tarzan could but stand facing that hideous charge. In his right hand he grasped his hunting knife--a puny, futile thing indeed by comparison with the great rows of mighty teeth which lined Sheeta's powerful jaws, and the sharp talons encased within his padded paws; yet the young Lord Greystoke faced it with the same courageous resignation with which some fearless ancestor went down to defeat and death on Senlac Hill by Hastings. was

From safety points in the trees the great apes

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another direction; but all day there rose one after another, above the threshold of his objective mind, memory portraits of Sabor, of Momaya, and of Teeka--a lioness, a cannibal, and a she-ape, yet to the ape-man they were identical through motherhood.

It was noon of the third day when Momaya came within sight of the cave of Bukawai, the unclean. The old witch-doctor had rigged a framework of interlaced boughs to close the mouth of the cave from predatory beasts. This was now set to one side, and the black cavern beyond yawned mysterious and repellent. Momaya shivered as from a cold wind of the rainy season. No sign of life appeared about the cave, yet Momaya experienced that uncanny sensation as of unseen eyes regarding her malevolently. Again she shuddered. She tried to force her unwilling feet onward toward the cave, when from its depths issued an uncanny sound that was neither brute nor human, a weird sound

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and to hunt for--someone to caress; but now his dream was shattered. Something hurt within his breast. He placed his hand over his heart and wondered what had happened to him. Vaguely he attributed his pain to Teeka. The more he thought of Teeka as he had last seen her, caressing Taug, the more the thing within his breast hurt him.

Tarzan shook his head and growled; then on and on through the jungle he swung, and the farther he traveled and the more he thought upon his wrongs, the nearer he approached becoming an irreclaimable misogynist.

Two days later he was still hunting alone- very morose and very unhappy; but he was determined never to return to the tribe. He could not bear the thought of seeing Taug and Teeka always together. As he swung upon a great limb Numa, the lion, and Sabor, the lioness, passed beneath him, side by side, and Sabor

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depth of her wild little heart she had longed for the day when the jungle grasses would be reddened with the blood of mortal combat for her fair sake.

So now she squatted upon her haunches and insulted both her admirers impartially. She hurled taunts at them for their cowardice, and called them vile names, such as Histah, the snake, and Dango, the hyena. She threatened to call Mumga to chastise them with a stick- Mumga, who was so old that she could no longer climb and so toothless that she was forced to confine her diet almost exclusively to bananas and grub-worms.

The apes who were watching heard and laughed. Taug was infuriated. He made a sudden lunge for Tarzan, but the ape-boy leaped nimbly to one side, eluding him, and with the quickness of a cat wheeled and leaped back again to close quarters. His hunting knife was raised above his

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all the myriad wonders which heretofore he had but taken for granted.

What made the flower open? What made it grow from a tiny bud to a full-blown bloom? Why was it at all? Why was he? Where did Numa, the lion, come from? Who planted the first tree? How did Goro get way up into the darkness of the night sky to cast his welcome light upon the fearsome nocturnal jungle? And the sun! Did the sun merely happen there?

Why were all the peoples of the jungle not trees? Why were the trees not something else? Why was Tarzan different from Taug, and Taug different from Bara, the deer, and Bara different from Sheeta, the panther, and why was not Sheeta like Buto, the rhinoceros? Where and how, anyway, did they all come from--the trees, the flowers, the insects, the countless creatures of the jungle?

Quite unexpectedly an idea popped into

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the blood-madness of battle that they failed to note the approach of the giant tusker.

Upon these Tantor charged, trumpeting furiously. Above them he stopped, his sensitive trunk weaving among them, and there, at the bottom, he found Tarzan, bloody, but still battling.

A warrior turned his eyes upward from the melee. Above him towered the gigantic bulk of the pachyderm, the little eyes flashing with the reflected light of the fires--wicked, frightful, terrifying. The warrior screamed, and as he screamed, the sinuous trunk encircled him, lifted him high above the ground, and hurled him far after the fleeing crowd.

Another and another Tantor wrenched from the body of the ape-man, throwing them to right and to left, where they lay either moaning or very quiet, as death came slowly or at once.

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strange, inexplicable force stayed his hand--a force inexplicable to him, perhaps, because of his ignorance of his own origin and of all the forces of humanitarianism and civilization that were his rightful heritage because of that origin.

So today, instead of staying his hand until a less formidable feast found its way toward him, Tarzan dropped his new noose about the neck of Horta, the boar. It was an excellent test for the untried strands. The angered boar bolted this way and that; but each time the new rope held him where Tarzan had made it fast about the stem of the tree above the branch from which he had cast it.

As Horta grunted and charged, slashing the sturdy jungle patriarch with his mighty tusks until the bark flew in every direction, Tarzan dropped to the ground behind him. In the ape man's hand was the long, keen blade that had been his constant companion since that distant

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him--something new to Tarzan of the Apes in relation to an enemy. It was pity--pity for a poor, frightened, old man.

Tarzan rose and turned away, leaving Mbonga, the chief, unharmed.

With head held high the ape-man walked through the village, swung himself into the branches of the tree which overhung the palisade and disappeared from the sight of the villagers.

All the way back to the stamping ground of apes, Tarzan sought for an explanation of the the strange power which had stayed his hand and prevented him from slaying Mbonga. It was as though someone greater than he had commanded him to spare the life of the old man. Tarzan could not understand, for he could conceive of nothing, or no one, with the authority to dictate to him what he should do, or what he should refrain from doing.

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lightning and the rain and the thunder came from Goro, the moon. He knew this, he said, because the Dum-Dum always was danced in the light of Goro. This reasoning, though entirely satisfactory to Numgo and Mumga, failed fully to convince Tarzan. However, it gave him a basis for further investigation along a new line. He would investigate the moon.

That night he clambered to the loftiest pinnacle of the tallest jungle giant. The moon was full, a great, glorious, equatorial moon. The ape-man, upright upon a slender, swaying limb, raised his bronzed face to the silver orb. Now that he had clambered to the highest point within his reach, he discovered, to his surprise, that Goro was as far away as when he viewed him from the ground. He thought that Goro was attempting to elude him.

"Come, Goro!" he cried, "Tarzan of the Apes will not harm you!" But still the moon held aloof.

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scratched the more tender surfaces beneath the great ears, he talked to Tantor of the gossip of the jungle as though the great beast understood every word that he said.

Much there was which Tarzan could make Tantor understand, and though the small talk of the wild was beyond the great, gray dreadnaught of the jungle, he stood with blinking eyes and gently swaying trunk as though drinking in every word of it with keenest appreciation. As a matter of fact it was the pleasant, friendly voice and caressing hands behind his ears which he enjoyed, and the close proximity of him whom he had often borne upon his back since Tarzan, as a little child, had once fearlessly approached the great bull, assuming upon the part of the pachyderm the same friendliness which filled his own heart.

In the years of their association Tarzan had discovered that he possessed an inexplicable

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long, sinuous leap, the coils of the ape-boy's grass rope shot swiftly through the air, straightening into a long thin line as the open noose hovered for an instant above the savage head and the snarling jaws. Then it settled--clean and true about the tawny neck it settled, and Tarzan, with a quick twist of his rope-hand, drew the noose taut, bracing himself for the shock when Sheeta should have taken up the slack.

Just short of Teeka's glossy rump the cruel talons raked the air as the rope tightened and Sheeta was brought to a sudden stop--a stop that snapped the big beast over upon his back. Instantly Sheeta was up--with glaring eyes, and lashing tail, and gaping jaws, from which issued hideous cries of rage and disappointment.

He saw the ape-boy, the cause of his discomfiture, scarce forty feet before him, and Sheets charged.

Teeka was safe now; Tarzan saw to that by a

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way, but continued on through the jungle more in search of adventure than of food, for today he was restless. And so it came that he turned his footsteps toward the village of Mbonga, the black chief, whose people Tarzan had baited remorselessly since that day upon which Kulonga, the chief's son, had slain Kala.

A river winds close beside the village of the black men. Tarzan reached its side a little below the clearing where squat the thatched huts of the Negroes. The river life was ever fascinating to the ape-man. He found pleasure in watching the ungainly antics of Duro, the hippopotamus, and keen sport in tormenting the sluggish crocodile, Gimla, as he basked in the sun. Then, too, there were the shes and the balus of the black men of the Gomangani to frighten as they squatted by the river, the shes with their meager washing, the balus with their primitive toys.

This day he came upon a woman and her

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14 ANTIVIRAL THERAPY

COVID-19 is an infectious disease caused by SARS-COV-2, which is also termed the novel coronavirus and is diligently associated with the SARS virus. The Ministry of Science and Technology from the People's Republic of China declared three potential antiviral medicines suitable for treating COVID-19. Those three medicines are, namely, Favilavir, chloroquine phosphate and remdesivir. A clinical trial was conducted to test the efficacy of those three drugs, and the results proved that out of the three medicines above only Favilavir is effective in treating the patients with novel coronavirus. The remaining two drugs were effective in treating malaria.6 62

Likewise a study carried out in the United States by the National Institute of Health proved that remdesivir is effective in treating the Middle East respiratory syndrome coronavirus (MERS COV), which is also a type of coronavirus that was transmitted from monkeys. The drug remdesivir was also used in the United States for treating the patients with COVID-19. There has been a proposal to use the combination of protease inhibitors lopinavir-ritonavir for treating the patients affected by COVID-19.62

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

(96.7%), and S genes (90.4%). The RBD of S protein in CoV isolated from pangolin was almost identical

(one amino acid difference) to that of SARS-CoV-2. A comparison of the genomes suggests recombination between pangolin-CoV-like viruses with the bat-CoV-RaTG13-like virus. All this suggests the potential of pangolins to act as the intermediate host of SARS-CoV-2 (145).

Human-wildlife interactions, which

are increasing in the context of climate change (142), are further considered high risk and responsible for the emergence of SARS-CoV. COVID-19 is also suspected of having a similar mode of origin. Hence, to prevent the occurrence of another zoonotic spillover (1), exhaustive coordinated efforts are needed to identify the high-risk pathogens harbored by wild animal populations, conducting surveillance among the people who are susceptible to zoonotic spillover events (12), and to improve the biosecurity measures associated with the wildlife trade (146). The serological surveillance studies conducted in people living in proximity to bat caves had earlier identified the serological confirmation of SARS related CoVs in humans. People living at the wildlife-human interface, mainly in rural China, are regularly exposed to SARS-related CoVs (147). These findings will not have any significance until a

appeared asymptomatic. 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 infection in cat populations in Wuhan, although the potential of SARS-CoV-2 transmission from cats to humans is currently uncertain46.

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 dog11,43,48,49. 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 differ ent animals may indicate their different susceptibilities to SARS-CoV-2 infection. The S1 subunit of a corona virus 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 S1 C-terminal domain of SARS-CoV-2 as the RBD, which has a key role in virus entry and is the target of neu tralizing antibodies50,51 (FIG. 3a). The RBM mediates con tact 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

polymorphism at nucleotide position 28,144, which results in amino acid substitution of Ser for Lys at residue 84 of the ORF8 protein. Those variants with this muta tion make up a single subclade labelled as 'clade S'33,34. Currently, however, the available sequence data are not sufficient to interpret the early global transmission his tory of the virus, and travel patterns, founder effects and public health measures also strongly influence the spread of particular lineages, irrespective of potential biological differences between different virus variants.

Animal host and spillover

Bats are important natural hosts of alphacoronavi ruses and betacoronaviruses. The closest relative to SARS-CoV-2 known to date is a bat coronavirus detected in Rhinolophus affinis from Yunnan province, China, named 'RaTG13', whose full-length genome sequence is 96.2% identical to that of SARS-CoV-2 (REF.). This bat virus shares more than 90% sequence identity with SARS-CoV-2 in all ORFs throughout the genome, including the highly variable S and ORF8 (REF). Phylogenetic analysis confirms that SARS-CoV-2 closely clusters with RaTG13 (FIG. 2). The high genetic similarity between SARS-CoV-2 and RaTG13 supports the hypothesis that SARS-CoV-2 likely originated from bats 35. Another related coronavirus has been reported more recently in a Rhinolophus malayanus bat sampled in Yunnan This novel hat virus denoted 'RmYN02'

residues for receptor binding40 (FIG. 3b). In comparison with the Guangdong strains, pangolin coronaviruses reported from Guangxi are less similar to SARS-CoV-2, with 85.5% genome sequence identity. The repeated occurrence of SARS-CoV-2-related coronavirus infec tions in pangolins from different smuggling events suggests that these animals are possible hosts of the viruses. However, unlike bats, which carry coronaviruses healthily, the infected pangolins showed clinical signs and histopathological changes, including interstitial pneumonia and inflammatory cell infiltration in diverse organs 40. These abnormalities suggest that pangolins are unlikely to be the reservoir of these coronaviruses but more likely acquired the viruses after spillover from the natural hosts.

An intermediate host usually plays an important role in the outbreak of bat-derived emerging coronaviruses; for example, palm civets for SARS-CoV and dromedary camels for MERS-CoV. The virus strains carried by these two intermediate hosts were almost genetically identi cal to the corresponding viruses in humans (more than 99% genome sequence identity)'. Despise an RBD that is virtually identical to that of SARS-CoV-2, the pangolin coronaviruses known to date have no more than 92% genome identity with SARS-CoV-2 (REF.42). The avail able data are insufficient to interpret pangolins as the intermediate host of SARS-CoV-2. So far, no evidence has shown that pangolins were directly involved in the emergence of SARS-CoV-2.

Inhibition of virus replication. Replication inhibitors

include remdesivir (GS-5734), favilavir (T-705), riba virin, lopinavir and ritonavir. Except for lopinavir and ritonavir, which inhibit 3CLpro, the other three all target RdRp12 (FIG. 5). Remdesivir has shown activity against 128,135 SARS-CoV-2 in vitro and in vivo 128,136. A clinical study revealed a lower need for oxygen support in patients with COVID-19 (REF 137). Preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT) clinical trial by the National Institute of Allergy and Infectious Diseases (NIAID) reported that remdesivir can shorten the recovery time in hospitalized adults with COVID-19 by a couple days compared with placebo, but the differ ence in mortality was not statistically significant¹38. The FDA has issued an emergency use authorization for rem desivir for the treatment of hospitalized patients with severe COVID-19. It is also the first approved option by the European Union for treatment of adults and adoles cents with pneumonia requiring supplemental oxygen. Several international phase III clinical trials are contin uing to evaluate the safety and efficacy of remdesivir for the treatment of COVID-19.

Favilavir (T-705), which is an antiviral drug devel oped in Japan to treat influenza, has been approved in China, Russia and India for the treatment of COVID-19. A clinical study in China showed that favilavir signif icantly reduced the signs of improved disease signs on chest imaging and shortened the time to viral clearance¹39. A preliminary report in Japan showed rates of clinical improvement of 73.8% and 87.8% from the start of favilavir therapy in patients with mild COVID-19 at 7 and 14 days, respectively, and 40.1% and 60.3% in patients with severe COVID-19 at 7 and 14 days,

Splits Tree phylogeny analysis.

In the unrooted phylogenetic tree of different betacoronaviruses 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 Splits Tree 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 placed 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 Orthocoronavirinae subfamily and is entirely different from the viruses

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 103 on 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).

8 PREVENTION

The WHO and other agencies such as the CDC have published protective measures to mitigate the spread of COVID-19. This involves frequent hand washing with handwash containing 60% of alcohol and soap for at least 20 seconds.

Another important measure is avoiding close contact with sick people and keeping a social distance of 1 metre always to everyone who is coughing and sneezing. Not touching the nose, eyes and mouth was also suggested. While coughing or sneezing, covering the mouth and nose with a cloth/tissue or the bent elbow is advised. Staying at home is recommended for those who are sick, and wearing a facial mask is advised when going out among people. Furthermore, it is recommended to clean and sterilise frequently touched surfaces such as phones and doorknobs on a daily basis.51, 52 Staying at home as much as possible is advisable for those who are at higher risk for severe illness, to minimise the risk of exposure to COVID-19 during outbreaks.53

prevailing chronic medical conditions such as

lung disease, heart failure, cancer, cerebrovascular disease, renal disease, diabetes, liver disease and immunocompromising conditions and pregnancy are risk factors for developing severe illness. Management includes implementation of prevention and control measures and supportive therapy to manage the complications, together with advanced organ support. 57

Corticosteroids must be avoided unless specified for chronic obstructive pulmonary disease exacerbation or septic shock, as it is likely to prolong viral replication as detected in MERS-CoV patients.58

12 EARLY SUPPORTIVE THERAPY AND MONITORING

Management of patients with suspected or documented COVID-19 consists of ensuring appropriate infection control and supportive care. WHO and the CDC posted clinical guidance for COVID-19.59

Immediate therapy of add-on oxygen must be started for patients with severe acute respiratory infection (SARI) and respiratory

with SARS and MERS (117).

SARS-CoV-2 invades the lung parenchyma, resulting in severe interstitial inflammation of the lungs. This is evident on computed tomography (CT) images as ground-glass opacity in the lungs. This lesion initially involves a single lobe but later expands to multiple lung lobes (118). The histological assessment of lung biopsy samples obtained from COVID-19-infected patients revealed diffuse alveolar damage, cellular fibromyxoid exudates, hyaline membrane formation, and desquamation of pneumocytes, indicative of acute respiratory distress syndrome (119). It was also found that the SARS-CoV-2-infected patients often have lymphocytopenia with or without leukocyte abnormalities. The degree of lymphocytopenia gives an idea about disease prognosis, as it is found to be positively correlated with disease severity (118). Pregnant women are considered to have a higher risk of getting infected by COVID-19. The coronaviruses can cause adverse outcomes for the fetus, such as intrauterine growth restriction, spontaneous abortion, preterm delivery, and perinatal death.

Nevertheless, the possibility of intrauterine

maternal-fetal transmission (vertical transmission) of

CoVs is low and was not seen during either the

SARS- or MERS-CoV outbreak (120). However,

(36, 59). Nevertheless, for SARS and MERS, Civer

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

Coronavirus 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, ppla and pplab, are initially produced from ORF1a/b by a -1 frameshift between ORFla 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

populations. The in vitro and in vivo studies carried

out on the isolated virus confirmed that there is a potential risk for the reemergence of SARS-CoV infection from the viruses that are currently circulating in the bat population (105).

CLINICAL PATHOLOGY OF SARS-CoV-2 (COVID-19)

The disease caused by SARS-CoV-2 is also named severe specific contagious pneumonia (SSCP), Wuhan pneumonia, and, recently, COVID 19 (110). Compared to SARS-CoV, SARS-CoV-2 has less severe pathogenesis but has superior transmission capability, as evidenced by the rapidly increasing number of COVID-19 cases (111). The incubation period of SARS-CoV-2 in familial clusters was found to be 3 to 6 days (112). The mean incubation period of COVID-19 was found to be 6.4 days, ranging from 2.1 to 11.1 days (113). Among an early affected group of 425 patients, 59 years was the median age, of which more males were affected (114). Similar to SARS and MERS, the severity of this nCoV is high in age groups above 50 years (2, 115). Symptoms of COVID-19 include fever, cough, myalgia or fatigue, and, less commonly, headache, hemoptysis, and diarrhea (116, 282). Compared to the SARS-CoV-2-infected patients in Wuhan during

respectively140. However, this study did not include a control arm, and most of the trials of favilavir were based on a small sample size. For more reliable assess ment of the effectiveness of favilavir for treating COVID-19, large-scale randomized controlled trials should be conducted.

Lopinavir and ritonavir were reported to have in vitro inhibitory activity against SARS-CoV and MERS-CoV141,142. Alone, the combination of lopinavir

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 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 therapeutics/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

We assessed the nucleotide percent similarity using the MegAlign software program, where the similarity between the novel SARS-CoV-2 isolates was in the range of 99.4% to 100%. Among the other Serbecovirus CoV sequences, the novel SARS-CoV 2 sequences revealed the highest similarity to bat SL-COV, with nucleotide percent identity ranges between 88.12 and 89.65%. Meanwhile, earlier reported SARS-CoVs showed 70.6 to 74.9% similarity to SARS-CoV-2 at the nucleotide level. Further, the nucleotide percent similarity was 55.4%, 45.5% to 47.9%, 46.2% to 46.6%, and 45.0% to 46.3% to the other four subgenera, namely, Hibecovirus, Nobecovirus, Merbecovirus, and Embecovirus, respectively. The percent similarity index of current outbreak isolates indicates a close relationship between SARS-CoV-2 isolates and bat SL-COV, indicating a common origin. However, particular pieces of evidence based on further complete genomic analysis of current isolates are necessary to draw any conclusions, although it was ascertained that the current novel SARS-CoV-2 isolates belong to the subgenus Sarbecovirus in the diverse range of betacoronaviruses. Their possible ancestor was hypothesized to be from bat CoV strains, wherein bats might have played a crucial role in harboring this class of viruses.

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 individu als 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 retro spective studies116,120,121. However, the extent and dura tion of immune responses are still unclear, and available serological tests differ in their sensitivity and specific ity, 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 thera pies 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 var ious 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 therapeutics tracker). In the following sections, we summarize potential therapeutics against SARS-CoV-2 on the basis of published clinical data and experience.

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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

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) 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 its coronavirus to predecessors, COVID-19 has an Ro value that is greater than that of MERS (Ro< 1) (108) but less than that of SARS (Ro value of 2 to 5) (93). Still, to prevent further spread of disease at mass gatherings,

Encircled with an envelope containing viral nucleocapsid. The nucleocapsids in CoVs are arranged in helical symmetry, which reflects an atypical attribute in positive-sense RNA viruses (30). The electron micrographs of SARS-CoV-2 revealed a diverging spherical outline with some degree of pleomorphism, virion diameters varying from 60 to 140 nm, and distinct spikes of 9 to 12 nm, giving the virus the appearance of a solar corona (3). The COV genome is arranged linearly as 5'-leader-UTR replicase-structural genes (S-E-M-N)-3' UTR poly(A) (32). Accessory genes, such as 3a/b, 4a/b, and the hemagglutinin-esterase gene (HE), are also seen intermingled with the structural genes (30). SARS-CoV-2 has also been found to be arranged similarly and encodes several accessory proteins, although it lacks the HE, which is characteristic of some betacoronaviruses (31). The positive-sense genome of CoVs serves as the mRNA and is translated to polyprotein 1a/lab (ppla/lab) (33). A replication-transcription complex (RTC) is formed in double-membrane vesicles (DMVs) by nonstructural proteins (nsps), encoded by the polyprotein gene (34). Subsequently, the RTC synthesizes a nested set of subgenomic RNAs (sgRNAs) via discontinuous transcription (35).

themselves while examining such patients and practice hand hygiene frequently.

Suspected cases should be referred to government designated centres for isolation and testing (in Mumbai, at this time, it is Kasturba hospital). Commercial kits for testing are not yet available in India.

• Patients admitted with severe pneumonia and acute respiratory distress syndrome should be evaluated for travel history and placed under contact and droplet isolation. Regular decontamination of surfaces should be done. They should be tested for etiology using multiplex PCR panels if logistics permit and if no pathogen is identified, refer the samples for testing for SARS CoV-2.

having proven uses against other viral pathogens can be employed for SARS-CoV-2-infected patients. These possess benefits of easy accessibility and recognized pharmacokinetic and pharmacodynamic activities, stability, doses, and side effects (9). Repurposed drugs have been studied for treating CoV infections, like lopinavir/ritonavir, and interferon-1ẞ revealed in vitro anti-MERS-CoV action. The in vivo experiment carried out in the nonhuman primate model of common marmosets treated with lopinavir/ritonavir and interferon beta showed superior protective results in treated animals than in the untreated ones (190). A combination of these drugs is being evaluated to treat MERS in humans (MIRACLE trial) (191). These two protease inhibitors (lopinavir and ritonavir), in combination with ribavirin, gave encouraging clinical outcomes in SARS patients, suggesting their therapeutic values (165). However, in the current scenario, due to the lack of specific therapeutic agents against SARS CoV-2, hospitalized patients confirmed for the disease are given supportive care, like oxygen and fluid therapy, along with antibiotic therapy for managing secondary bacterial infections (192). Patients with novel coronavirus or COVID-19 pneumonia who are mechanically ventilated often require sedatives, analgesics, and even muscle

Abstract

There is a new public health crises threatening the world with the emergence and spread of 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, Hubei province, China in December 2019. There have been around 96,000 reported cases of coronavirus disease 2019 (COVID-2019) and 3300 reported deaths to date (05/03/2020). The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 d. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most people; in some (usually the elderly and those with

comorbidities) it may progross to

specifically in the respiratory tract will help to reduce virus-triggered immune pathologies in COVID-19 (209). The later stages of coronavirus induced inflammatory cascades are characterized by the release of proinflammatory interleukin-1 (IL-1) family members, such as IL-1 and IL-33. Hence, there exists a possibility that the inflammation associated with coronavirus can be inhibited by utilizing anti-inflammatory cytokines that belong to the IL-1 family (92). It has also been suggested that the actin protein is the host factor that is involved in cell entry and pathogenesis of SARS-CoV-2. Hence, those drugs that modulate the biological activity of this protein, like ibuprofen, might have some therapeutic application in managing the disease (174). The plasma angiotensin 2 level was found to be markedly elevated in COVID-19 infection and was correlated with viral load and lung injury. Hence, drugs that block angiotensin receptors may have potential for treating COVID-19 infection (121). A scientist from Germany, named Rolf Hilgenfeld, has been working on the identification of drugs for the treatment of coronaviral infection since the time of the first SARS outbreak (19).

The SARS-CoV S2 subunit has a significant function in mediating virus fusion that provides entry into the host cell. Heptad repeat 1 (HR1) and heptad

Coronaviruses in Humans-SARS, MERS,

and COVID-19

Coronavirus infection in humans is commonly associated with mild to severe respiratory diseases, with high fever, severe inflammation, cough, and internal organ dysfunction that can even lead to death (92). Most of the identified coronaviruses cause the common cold in humans. However, this changed when SARS-CoV was identified, paving the way for severe forms of the disease in humans (22). Our previous experience with the outbreaks of other coronaviruses, like SARS and MERS, suggests that the mode of transmission in COVID-19 as mainly human-to-human transmission via direct contact, droplets, and fomites (25). Recent studies have demonstrated that the virus could remain viable for hours in aerosols and up to days on surfaces; thus, aerosol and fomite contamination could play potent roles in the transmission of SARS-CoV-2 (257).

The immune response against coronavirus is vital to control and get rid of the infection. However, maladjusted immune responses may contribute to the immunopathology of the disease, resulting in impairment of pulmonary gas exchange. Understanding the interaction between CoVs and host innate immune systems could enlighten our

Inhibition of virus entry. SARS-CoV-2 uses ACE2 as the receptor and human proteases as entry activators; sub sequently it fuses the viral membrane with the cell mem brane and achieves invasion. Thus, drugs that interfere with entry may be a potential treatment for COVID-19. Umifenovir (Arbidol) is a drug approved in Russia and China for the treatment of influenza and other respira tory viral infections. It can target the interaction between the S protein and ACE2 and inhibit membrane fusion (FIG. 5). In vitro experiments showed that it has activity against SARS-CoV-2, and current clinical data revealed it may be more effective than lopinavir and ritonavir in treating COVID-19 (REFS 122,123). However, other clinical studies showed umifenovir might not improve the prog nosis of or accelerate SARS-CoV-2 clearance in patients with mild to moderate COVID-19 (REFS 124,125). Yet some ongoing clinical trials are evaluating its efficacy for COVID-19 treatment. Camostat mesylate is approved in Japan for the treatment of pancreatitis and postoper ative reflux oesophagitis. Previous studies showed that it can prevent SARS-CoV from entering cells by blocking TMPRSS2 activity and protect mice from lethal infection with SARS-CoV in a pathogenic mouse model (wild type mice infected with a mouse-adapted SARS-CoV strain) 126,127. Recently, a study revealed that camostat mesylate blocks the entry of SARS-CoV-2 into human lung cells. Thus, it can be a potential antiviral drug against SARS-CoV-2 infection, although so far there are not sufficient clinical data to support its efficacy.

6.5 Specimen collection and storage

A Nasopharyngeal and oropharyngeal swab should be collected using Dacron or polyester flocked swabs. It should be transported to the laboratory at a temperature of 4°C and stored in the laboratory between 4 and -70°C on the basis of the number of days and, in order to increase the viral load, both nasopharyngeal and oropharyngeal swabs should be placed in the same tube. Bronchoalveolar lavage and nasopharyngeal aspirate should be collected in a sterile container and transported similarly to the laboratory by maintain a temperature of 4°C.

Sputum samples, especially from the lower respiratory tract, should be collected with the help of a sterile container and stored, whereas tissue from a biopsy or autopsy should be collected using a sterile container along with saline. However, both should be stored in the laboratory at a temperature that ranges between 4 and -70°C. Whole blood for detecting the antigen, particularly in the first week of illness, should be collected in a collecting tube and stored in the laboratory between 4 and -70°C. Urine samples must also be collected using a sterile container and stored

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

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 alveo lar 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 res piratory distress syndrome and respiratory failure, which is considered the main cause of death in patients with COVID-19 (REFS6061). Patients of older age (>60 years) and with serious pre-existing diseases have a greater risk of developing acute respiratory distress syndrome and death62-64 (FIG. 4). Multiple organ failure has also been reported in some COVID-19 cases9,13,65

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 shown in some cases. Immunohistochemistry assays detected SARS-CoV-2 antigen in the upper airway, bronchiolar epithelium and submucosal gland epithelium, as well as in type I and type II pneumocytes, alveolar macrophages and hyaline membranes in the lungs 13,60,66,67

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 hamsters43.48.68-74. In non-human primate animal mod els, most species display clinical features similar to those of patients with COVID-19, including virus shedding, virus replication and host responses to SARS-CoV-2 infection 69,72,73, For example, in the rhesus macaque model, high viral loads were detected in the upper and

subfamily and is entirely amerent from the viruses

responsible for MERS-CoV and SARS-CoV (3). The newly emerged SARS-CoV-2 is a coronavirus (2). The genome sequences of SARS group 2B 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

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

Animal Models and Cell Cultures

For evaluating the potential of vaccines and therapeutics against CoVs, including SARS-CoV, MERS-CoVs, and the presently emerging SARS CoV-2, suitable animal models that can mimic the clinical disease are needed (211, 212). Various animal models were assessed for SARS- and MERS CoVs, such as mice, guinea pigs, golden Syrian hamsters, ferrets, rabbits, nonhuman primates like rhesus macaques and marmosets, and cats (185, 213-218). The specificity of the virus to hACE2 (receptor of SARS-CoV) was found to be a significant barrier in developing animal models. Consequently, a SARS-CoV transgenic mouse model has been developed by inserting the hACE2 gene into the mouse genome (219). The inability of MERS-CoV to replicate in the respiratory tracts of animals (mice, hamsters, and ferrets) is another limiting factor. However, with genetic engineering, a 288-330++ MERS-CoV genetically modified mouse model was developed and now is in use for the assessment of novel drugs and vaccines against MERS-CoV (220). In the past, small animals (mice or hamsters) have been targeted for being closer to a humanized structure, such as mouse DPP4 altered with human DPP4 (hDPP4), hDPP4-transduced mice, and hDPP4-Tg mice (transgenic for expressing

primary anti-genic epitopes mainly those recognised by neutralising antibodies. The spike S-protein being in a spike form is subjected to a structural rearrangement process so that fusing the outer membrane of the virus with the host cell membrane becomes easier. 19, 20 Recent SARS-COV work has also shown that the membrane exopeptidase ACE enzyme (angiotensin-converting enzyme) functions as a COVID-19 receptor to enter the human cell.21

consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive molecular tests on repeat testing [22].

Differential Diagnosis [21]

The differential diagnosis includes all types of respiratory viral infections [influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, non COVID 19 coronavirus], atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine lab tests. Therefore travel history becomes important. However, as the epidemic spreads, the travel history

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

assessed intrauterine vertical transmission of COVID-19 infection in nine infants born to infected mothers, found that none of the infants tested positive for the virus.45 Likewise, there was no evidence of intrauterine infection caused by vertical transmission in the SARS and MERS epidemics.43

The CDC asserts that infants born to mothers with confirmed COVID-19 are considered persons under investigation (PUI) and should be temporarily separated from the mother and isolated.4

7.1 Breastfeeding and infant care

The data available to date is limited and cannot confirm whether or not COVID-19 can be transmitted through breast milk.40 Assessing the presence of COVID-19 in breast milk samples from six patients showed negative result.45 The CDC points out that in case of a confirmed or suspected COVID-19 infection, the decision of whether or how to start or continue breastfeeding should be made by the mother in collaboration with the family and healthcare practitioners.47 Careful precautions need to be taken by the mother to prevent transmitting the disease to her infant through respiratory droplets during breastfeeding. This includes wearing a facemask and practising hand

(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

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

countries have a fragile health system that can be crippled in the event of an outbreak. Effective management of COVID-19 would be difficult for low-income countries due to their inability to respond rapidly due to the lack of an efficient health care system (65). Controlling the imported cases is critical in preventing the spread of COVID-19 to other countries that have not reported the disease until now. The possibility of an imported case of COVID-19 leading to sustained human-to-human transmission was estimated to be 0.41. This can be reduced to a value of 0.012 by decreasing the mean time from the onset of symptoms to hospitalization and can only be made possible by using intense disease surveillance systems (235). The silent importations of infected individuals (before the manifestation of clinical signs) also contributed significantly to the spread of disease across the major cities of the world. Even though the travel ban was implemented in Wuhan (89), infected persons who traveled out of the city just before the imposition of the ban might have remained undetected and resulted in local outbreaks (236). Emerging novel diseases like COVID-19 are difficult to contain within the country of origin, since globalization has led to a world without borders. Hence, international collaboration plays a vital role

countries. Large-scale screening programs might

help us to control the spread of this virus. However, this is both challenging as well as time-consuming due to the present extent of infection (226). The current scenario demands effective implementation of vigorous prevention and control strategies owing to the prospect of COVID-19 for nosocomial infections (68). Follow-ups of infected patients by telephone on day 7 and day 14 are advised to avoid any further unintentional spread or nosocomial transmission (312). The availability of public data sets provided by independent analytical teams will act as robust evidence that would guide us in designing interventions against the COVID-19 outbreak. Newspaper reports and social media can be used to analyze and reconstruct the progression of an outbreak. They can help us to obtain detailed patient level data in the early stages of an outbreak (227). Immediate travel restrictions imposed by several countries might have contributed significantly to preventing the spread of SARS-CoV-2 globally (89, 228). Following the outbreak, a temporary ban was imposed on the wildlife trade, keeping in mind the possible role played by wild animal species in the origin of SARS-CoV-2/COVID-19 (147). Making a permanent and bold decision on the trade of wild animal species is necessary to prevent the possibility

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 2/3/2020, 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

COVID-19 patients showing severe signs are treated symptomatically along with oxygen therapy. In such cases where the patients progress toward respiratory failure and become refractory to oxygen therapy, mechanical ventilation is necessitated. The COVID-19-induced septic shock can be managed by providing adequate hemodynamic support (299). Several classes of drugs are currently being evaluated for their potential therapeutic action against SARS-CoV-2. Therapeutic agents that have anti-SARS-CoV-2 activity can be broadly classified into three categories: drugs that block virus entry into the host cell, drugs that block viral replication as well as its survival within the host cell, and drugs that attenuate the exaggerated host immune response (300). An inflammatory cytokine storm is commonly seen in critically ill COVID-19 patients. Hence, they may benefit from the use of timely anti-inflammation treatment. Anti-inflammatory therapy using drugs like glucocorticoids, cytokine inhibitors, JAK inhibitors, and chloroquine/hydroxychloroquine should be done only after analyzing the risk/benefit ratio in COVID-19 patients (301). There have not been any studies concerning the application of nonsteroidal anti-inflammatory drugs (NSAID) to COVID-19-infected patients. However, reasonable pieces of evidence are available that link NSAID

These findings will not have any significance until a significant outbreak occurs due to a virus-like SARS-CoV-2.

There is a steady increase in the reports of COVID-19 in companion and wild animals around the world. Further studies are required to evaluate the potential of animals (especially companion animals) to serve as an efficient reservoir host that can further alter the dynamics of human-to-human transmission (330). To date, two pet dogs (Hong Kong) and four pet cats (one each from Belgium and Hong Kong, two from the United States) have tested positive for SARS-CoV-2 (335). The World Organization for Animal Health (OIE) has confirmed the diagnosis of COVID-19 in both dogs and cats due to human-to-animal transmission (331). The similarity observed in the gene sequence of SARS CoV-2 from an infected pet owner and his dog further confirms the occurrence of human-to-animal transmission (333). Even though asymptomatic, feline species should be considered a potential transmission route from animals to humans (326). However, currently, there are no reports of SARS CoV-2 transmission from felines to human beings. Based on the current evidence, we can conclude that cats are susceptible to SARS-CoV-2 and can get infected by human beings. However, evidence of cat

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

systems con egiten ar

understanding of the lung inflammation associated with this infection (24).

SARS is a viral respiratory disease caused by a formerly unrecognized animal CoV that originated from the wet markets in southern China after adapting to the human host, thereby enabling transmission between humans (90). The SARS outbreak reported in 2002 to 2003 had 8,098 confirmed cases with 774 total deaths (9.6%) (93). The outbreak severely affected the Asia Pacific region, especially mainland China (94). Even though the case fatality rate (CFR) of SARS-CoV-2 (COVID-19) is lower than that of SARS-CoV, there exists a severe concern linked to this outbreak due to its epidemiological similarity to influenza viruses (95, 279). This can fail the public health system, resulting in a pandemic (96).

MERS is another respiratory disease that was first reported in Saudi Arabia during the year 2012. The disease was found to have a CFR of around 35% (97). The analysis of available data sets suggests that the incubation period of SARS-CoV-2, SARS-CoV, and MERS-CoV is in almost the same range. The longest predicted incubation time of SARS-CoV-2 is 14 days. Hence, suspected individuals are isolated for 14 days to avoid the risk of further spread (98). Even though a high similarity has been reported

developed for rapid and colorimetric detection of this virus (354). RT-LAMP serves as a simple, rapid, and sensitive diagnostic method that does not require sophisticated equipment or skilled personnel (349). An interactive web-based dashboard for tracking SARS-CoV-2 in a real-time mode has been designed (238). A smartphone-integrated home-based point of-care testing (POCT) tool, a paper-based POCT combined with LAMP, is a useful point-of-care diagnostic (353). An Abbott ID Now COVID-19 molecular POCT-based test, using isothermal nucleic acid amplification technology, has been designed as a point-of-care test for very rapid detection of SARS-CoV-2 in just 5 min (344). A CRISPR-based SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) diagnostic for rapid detection of SARS-CoV-2 without the requirement of specialized instrumentation has been reported to be very useful in the clinical diagnosis of COVID-19 (360). A CRISPR-Cas 12-based lateral flow assay also has been developed for rapid detection of SARS-CoV-2 (346). Artificial intelligence, by means of a three dimensional deep-learning model, has been developed for sensitive and specific diagnosis of COVID-19 via CT images (332).

Tracking and mapping of the rising incidence rates, disease outbreaks, community spread,

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 January15. On 30 January, the WHO declared the novel coronavirus outbreak a public health emergency of inter national concern¹6. 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 countryside¹8. Owing to these measures, the daily number of new cases in China started to decrease steadily.

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. The high transmission efficiency of SARS-CoV-2 and the abun dance of international travel enabled rapid worldwide spread of COVID-19. On 11 March 2020, the WHO officially characterized the global COVID-19 out break as a pandemic20. 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 dash board of the Center for System Science and Engineering at Johns Hopkins University, as of 11 August 2020,

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 (IFN) and RNA interference (62). Compared to that of SARS-COV, the N protein of SARS-CoV-2 possess five amino acid mutations, where two are in the intrinsically dispersed region (IDR; positions 25 and 26), one each in the NTD (position 103), LKR (position 217), and CTD (position 334) (16).

nsps and Accessory Proteins

mice, and hDPP4-Tg mice (transgenic for expressing hDPP4) for MERS-CoV infection (221). The CRISPR-Cas9 gene-editing tool has been used for inserting genomic alterations in mice, making them susceptible to MERS-CoV infection (222). Efforts are under way to recognize suitable animal models for SARS-CoV2/COVID-19, identify the receptor affinity of this virus, study pathology in experimental animal models, and explore virus-specific immune responses and protection studies, which together would increase the pace of efforts being made for developing potent vaccines and drugs to counter this emerging virus. Cell lines, such as monkey epithelial cell lines (LLC-MK2 and Vero-B4), goat lung cells, alpaca kidney cells, dromedary umbilical cord cells, and advanced ex vivo three-dimensional tracheobronchial tissue, have been explored to study human CoVs (MERS-CoV) (223, 224). Vero and Huh-7 cells (human liver cancer cells) have been used for isolating SARS-CoV-2 (194).

Recently, an experimental study with rhesus monkeys as animal models revealed the absence of any viral loads in nasopharyngeal and anal swabs, and no viral replication was recorded in the primary tissues at a time interval of 5 days post-reinfection in reexposed monkeys (274). The subsequent virological, radiological, and pathological

But the moon made no answer to the boasting of the ape-man, and when a cloud came and obscured her face, Tarzan thought that Goro was indeed afraid, and was hiding from him, so he came down out of the trees and awoke Numgo and told him how great was Tarzan--how he had frightened Goro out of the sky and made him tremble. Tarzan spoke of the moon as HE, for all things large or awe inspiring are male to the ape folk.

Numgo was not much impressed; but he was very sleepy, so he told Tarzan to go away and leave his betters alone.

"But where shall I find God?" insisted Tarzan. "You are very old; if there is a God you must have seen Him. What does He look like? Where does He live?"

"I am God," replied Numgo. "Now sleep and disturb me no more."

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counterpart of Sabor, the lioness. The males and the females differed, it was true; but not with such differences as existed between Tarzan and Teeka.

Tarzan was puzzled. There was something wrong. His arm dropped from the shoulder of Teeka. Very slowly he drew away from her. She looked at him with her head cocked upon one side. Tarzan rose to his full height and beat upon his breast with his fists. He raised his head toward the heavens and opened his mouth. From the depths of his lungs rose the fierce, weird challenge of the victorious bull ape. The tribe turned curiously to eye him. He had killed nothing, nor was there any antagonist to be goaded to madness by the savage scream. No, there was no excuse for it, and they turned back to their feeding, but with an eye upon the ape man lest he be preparing to suddenly run amuck.

As they watched him they saw him swing

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young, feminine loveliness. Or at least so thought Tarzan of the Apes, who squatted upon a low-swinging branch in a near-by tree and looked down upon her.

Just to have seen him there, lolling upon the swaying bough of the jungle-forest giant, his brown skin mottled by the brilliant equatorial sunlight which percolated through the leafy canopy of green above him, his clean-limbed body relaxed in graceful ease, his shapely head partly turned in contemplative absorption and his intelligent, gray eyes dreamily devouring the object of their devotion, you would have thought him the reincarnation of some demigod of old.

You would not have guessed that in infancy he had suckled at the breast of a hideous, hairy she-ape, nor that in all his conscious past since his parents had passed away in the little cabin by the landlocked harbor at the jungle's verge, he had known no other associates than the sullen

Tarzan's fertile brain evolved. Tarzan scratched his head, running his fingers deep into the shock of black hair which framed his shapely, boyish face--he scratched his head and sighed. Teeka's new-found beauty became as suddenly his despair. He envied her the handsome coat of hair which covered her body. His own smooth, brown hide he hated with a hatred born of disgust and contempt. Years back he had harbored a hope that some day he, too, would be clothed in hair as were all his brothers and sisters; but of late he had been forced to abandon the delectable dream.

Then there were Teeka's great teeth, not so large as the males, of course, but still mighty, handsome things by comparison with Tarzan's feeble white ones. And her beetling brows, and broad, flat nose, and her mouth! Tarzan had often practiced making his mouth into a little round circle and then puffing out his cheeks while he winked his eyes rapidly; but he felt that

he had heard stories of this bad, white forest god. It was he who had slain Kulonga and others of the warriors of Mbonga, the chief. It was he who entered the village stealthily, by magic, in the darkness of the night, to steal arrows and poison, and frighten the women and the children and even the great warriors. Doubtless this wicked god fed upon little boys. Had his mother not said as much when he was naughty and she threatened to give him to the white god of the jungle if he were not good? Little black Tibo shook as with ague.

"Are you cold, Go-bu-balu?" asked Tarzan, using the simian equivalent of black he-baby in lieu of a better name. "The sun is hot; why do you shiver?"

Tibo could not understand; but he cried for his mamma and begged the great, white god to let him go, promising always to be a good boy thereafter if his plea were granted. Tarzan shook

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had noted what Mbonga never would have thought of considering in the hunting of man- the wind. It was blowing in the same direction that Tarzan was proceeding, carrying to his delicate nostrils the odors which arose behind him. Thus it was that Tarzan knew that he was being followed, for even among the many stenches of an African village, the ape-man's uncanny faculty was equal to the task of differentiating one stench from another and locating with remarkable precision the source from whence it came.

He knew that a man was following him and coming closer, and his judgment warned him of the purpose of the stalker. When Mbonga, therefore, came within spear range of the ape man, the latter suddenly wheeled upon him, so suddenly that the poised spear was shot a fraction of a second before Mbonga had intended. It went a trifle high and Tarzan stooped to let it pass over his head; then he

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upward to be revenged upon Tarzan, but the ape man was otherwise engaged and did not wish to be interrupted. He was explaining again to Taug the depths of the latter's abysmal ignorance, and pointing out how much greater and mightier was Tarzan of the Apes than Taug or any other ape.

In the end he would release Taug, but not until Taug was fully acquainted with his own inferiority. And then the maddened bull came from beneath, and instantly Tarzan was transformed from a good-natured, teasing youth into a snarling, savage beast. Along his scalp the hair bristled: his upper lip drew back that his fighting fangs might be uncovered and ready. He did not wait for the bull to reach him, for something in the appearance or the voice of the attacker aroused within the ape-man a feeling of belligerent antagonism that would not be denied. With a scream that carried no human note, Tarzan leaped straight at the throat of the attacker.

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