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# Novel 2019-Coronavirus on New Year's Eve

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## Abstract

An ongoing apocalyptic outbreak of a new virus causing pneumonia-like clusters in Wuhan city, China, has gleamed the world. The outbreak, confirmed on the New Year's Eve 2020, has known no boundaries since then. The number has surpassed that of Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS), and is uninterruptedly escalating. Being an RNA virus, it has a propensity to mutate due to the low proofreading capacity of RNA-dependent RNA polymerase. Step-wise mutations have led to the gradual spillover of virus and after crossing the inter-species interface, the virus has adapted itself for a stable human-to-human transmission. The disease caused by severe acute respiratory syndrome coronavirus (CoV)-2 (SARS-CoV-2) can prove deadlier if the so-called 'super-spreading events' emerge with time. Recent research has shown the maximum homology of 99% of SARS-CoV-2 to pangolins associated coronavirus, owing to which these can serve as potential intermediate host. India is responding swiftly to the emergency situation, and the whole of the country is under lockdown since 25 March 2020, to ensure social distancing. All the international flights are padlocked and the travellers are being screened at airports and seaports via thermal sensors, and quarantine for a period of 14 days is recommended. Three hundred and forty-five patients across the country tested positive with six fatalities as of 22 March 2020. No specific anti-CoV drugs are currently available. Patients are being treated with protease drugs are inhibitors, remdesivir, chloroquine, angiotensin-converting enzyme 2 inhibitors, ivermectin, sarilumab and tocilizumab, though none of these is Food and Drug Administration approved and are undergoing trials. Preventive measures such as social distancing, quarantine, cough etiquettes, proper hand washing, cleaning and decontaminating the surfaces are the mainstay for curbing the transmission of this virus. The present review highlights the update of novel SARS-CoV-2 in context to the Indian scenario.

**Keywords:** Angiotensin-converting enzyme-2, bats, hand hygiene, quarantine, RNA-dependent RNA polymerase, SARS-CoV-2, social distancing, Wuhan

## INTRODUCTION

An ongoing apocalyptic outbreak of a new virus causing pneumonia-like clusters in Wuhan city, Central China, has glinted an alarm globally. The outbreak which was confirmed on the New Year's Eve 2020 has known no boundaries since then. A total of 316,662 people have been affected across 188 countries and one international conveyance, with 13,599 deaths (4.29% mortality) attributed to this novel coronavirus, currently designated as severe acute respiratory syndrome-coronavirus (CoV) (SARS-CoV-2), till 22 March 2020.<sup>[1]</sup> The number has already surpassed that of SARS and Middle East respiratory syndrome (MERS), and is continuously escalating uninterruptedly. The 'hotspot' for the origin of this virus was initially identified as a seafood market in Wuhan, Hubei district, in Mainland China,<sup>[2]</sup> and has gradually redeployed to Italy, which is witnessing the maximum number of cases and fatalities every passing day.<sup>[3]</sup>

## DISCOVERY AND EPIDEMIOLOGY

The first case, also referred to as zero or index case, reported to hospital with complaints of fever, cough and shortness of breath in December 2019. Consequently, after a cluster of 41 patients reported to healthcare facilities, an outbreak was suspected by the China National Health Commission on 30 December 2019, and the World Health Organization (WHO) declared pneumonia outbreak of unknown aetiology in Wuhan on 31 December 2019.<sup>[4]</sup> The virus was initially designated as

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2019-novel CoV (2019-nCoV), but has been renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, owing to the genetic homology with human SARS CoV. Consequently, on 11 February 2020, the WHO debuted the illness as coronavirus disease 2019 (COVID 19).<sup>[5]</sup> The 'hotspot' for the origin of this virus has been identified as a seafood market in Wuhan, Hubei district, in Mainland China. Subsequent to the seafood market being incriminated, it was shutdown on 1 January 2020. The most striking feature was the absence of exposure to the implicated seafood market in patient zero.<sup>[2]</sup> A total of 81,171 cases and 3277 deaths have been reported in China, and a total of forty healthcare workers (HCWs) have been affected till 22 March 2020. The maximum cases outside China have been reported from Italy (53,578 cases) followed by Spain (28,572 cases), the United States of America (26,908 cases), Germany (23,129 cases) and Iran (21,638 cases), as of 22 March 2020. The cases have also been reported from Switzerland, Taiwan, Malaysia, Australia, India, Vietnam, France, Macau, Norway, Canada, the Philippines, the UK, South Korea, Russia, Spain, Cambodia, Belgium, Finland, Sweden, Sri Lanka and Nepal.<sup>[1]</sup> An astronomical peak in the disease was illustrated from 10 February 2020 to 15 February 2020. Presently, Mainland China is contributing world's 25.54% of cases, however 74.46% of the cases are being reported from rest of the world, and the numbers are progressively intensifying.<sup>[1]</sup> On 11 March 2020, the World Health Organization (WHO) declared the disease as the first-ever pandemic caused by any CoV till date and has also contemplated a decline in the number of new cases in China, where the epidemic plateaued from 23 January to 2 February 2020.<sup>[6,7]</sup>

The history of exposure to the Wuhan seafood market was noted in only 65.85% (27/41) of the initially affected patients, thereby signposting the role of human-to-human transmission.<sup>[2]</sup> Two family clusters were identified initially, but subsequently, the infection has been reported from sundry individuals, with no history of travel to the hotspot region or exposure to any affected patients. This raises the possibility that the virus has mutated and well adapted itself for human transmission, like earlier-known coronaviruses.<sup>[4]</sup>

## AGENT

The causative agent, a positive-sense, single-stranded RNA virus, has an irregular shape with club-shaped spike projections and has been identified as a novel member of 2b-beta-CoV group of family *Coronaviridae* and order *Nidovirales*, which is comprised of other continuously circulating, endemic as well as epidemic strains.<sup>[8]</sup> The other members of the family include human CoV (HCoV) 229E, HCoV NL63, HCoV OC43, HCoV HKU 1, SARS-CoV and MERS-CoV, all of which have been found to have a zoonotic link. Bats have been implicated as natural host to all these CoVs, except HCoV-OC43 and HCoV-HKU1, in which rodents have been identified as the main reservoir.<sup>[8]</sup> Few of these CoVs are

continuously circulating, while some originate after a gradual spillover across animal-human interface.

Genomic sequencing of this novel virus has divulged 89% homology with SARS-related bat virus, belonging to the family *Betacoronaviridae*.<sup>[9]</sup> Being an RNA virus, it has a propensity to mutate, due to the low proofreading ability of RNA-dependent RNA polymerase (RdRp/VP), to acquire increased pathogenicity and ability for an efficient person-to-person transmission. This virus is different from the earlier SARS and MERS CoV, in better cultivation in human epithelial cell lines. The Victorian Infectious Disease Research Laboratory in Australia is credited with the first successful attempt to isolate this virus in cell lines.<sup>[10]</sup> Subsequently, the virus has been successfully isolated in China, the USA, Singapore, Japan and India. Vero-CCL81 cells and Vero E6 cell line expression are considered most permissive for the growth of virus.<sup>[11-18]</sup>

## Structure of severe acute respiratory syndrome-coronavirus-2

The SARS-CoV-2 genome encodes for both structural and non-structural proteins (nsps) and is around 29.8 kb nucleotides. The 5' terminus encodes for the open reading frame (ORF) 1ab, and the corresponding genes encode for polyproteins, pp1ab and pp1a proteins respectively. A total of 15 nsps are encoded by SARS-CoV-2, which include nsp1-nsp10 and nsp12-nsp16. These nsps encode for various viral factors and enzymes required for the replication of virus inside the host cell. The 3' terminus of the genome encodes for four major structural proteins, which include spike surface glycoprotein (S), small envelope protein (E), matrix protein (M), nucleocapsid protein (N) and eight accessory proteins. These structural proteins are building blocks of mature virions. The spike glycoprotein helps in binding to host cell receptor through angiotensin-converting enzyme 2 (ACE 2) as the main receptor.<sup>[19]</sup> This virus has more homology to SARS-CoV, enabling it to mutate rapidly towards human adaptation via enhanced binding to ACE2 receptors, which are used by both these viruses.<sup>[20]</sup> Currently, there are two prevalent evolution types for the same, L type (70%) and S (30%) type. L type is a derivative of S type and is much more aggressive and transmissible.<sup>[21]</sup> S type is, ancestral and less aggressive. It has been noted that in the initial phases of the pandemic, L strain was more prevalent especially in Wuhan, whose circulation wilted owing to the selection pressure and human interventions.<sup>[21]</sup> Although few studies have claimed variations in the genetic makeup of SARS-CoV-2 strains isolated from India, the same necessities auxiliary confirmation.<sup>[22]</sup> Recent discoveries have surfaced a functional furin polybasic cleavage site at S1-S2 interface via insertion of 12 nucleotides. This further assists in a prophesied acquisition of O-linked glycans adjacent to the site. These polybasic furin cleavage site and O-linked glycans provide an efficient cleavage by furins and proteases, thereby enhancing the viral infectivity due to snowballing cell-to-cell fusion, without disturbing the viral entry. The same phenomenon has been

noted in avian influenza, which transfigures the low pathogenic avian influenza to highly pathogenic avian influenza, crafting it more lethal. These polybasic furins have an auxiliary role in immune-evasion as well. The prophesied O-linked glycans help create a 'mucin-like domain' that enables guarding of the viral epitopes and the virus escapes the immune system, triggering noxious symptoms.<sup>[23]</sup>

## Host

All the age groups are susceptible to infection and the virus has infected everyone, from neonates to elderly population, with more severe infection being reported in elderly and immunocompromised patients, especially with comorbid conditions such as hypertension, diabetes and other cardiovascular diseases.<sup>[1,24,25]</sup> Three-fourths of the affected individuals in China were elderly and four of ten were immunosuppressed. The average age of the infected individuals has been noted to be 55.5 years and the maximum mortality has been noted to be nearly 75 years. Nearly 67.67% of the affected patients are males.<sup>[24,25]</sup> The oldest known person to be affected by this virus is 90 years old and the youngest one is a neonate, who was born to a coronavirus-positive mother in China in whom the virus was detected within 30 h of birth.<sup>[26]</sup> Nearly 4.7% of males have been affected, while the affected females account for 2.8% with higher case fatality rate (CFR) amongst the males (2.8:1.7). CFR has been reported to be maximum amongst elderly patients >80 years of age with a mortality rate of 21.9%. The most common comorbidities reported include cardiovascular diseases (13.2%), followed by diabetes (9.2%), chronic respiratory disease (8.0%), hypertension (8.4%) and cancers (7.6%).<sup>[1,27,28]</sup>

A study conducted in Wuhan has revealed <1% of cases amongst children <10 years of age, of the total 72,314 affected cases. Of the total 1391 paediatric samples tested, only 12.3% had confirmed COVID-19 infection. The median age was noted to be 6.7 years, with fever in 41.5% of cases. Most of the children presented with cough and pharyngeal erythema and had a milder clinical course. The astounding finding was absence of any clinical as well as radiological findings in 15.8% of the cases, while 12 children presented with radiological findings in the absence of any clinical symptoms. Three of the patients required ventilatory support, and all the three of these had underlying comorbidities in the form of hydronephrosis or intussusception or leukaemia. The most common radiological finding was the presence of ground-glass opacities and lymphopenia in 3.5% of the cases. Only one fatality was reported from a 10-month-old child, who collapsed within 4 weeks of admission, owing to the underlying intussusception and multiorgan dysfunction.<sup>[29]</sup> The same results have been reported by Lai *et al.*<sup>[30]</sup> A recent study has delineated the association of virus with blood group A. Zhao *et al.* have illustrated a higher susceptibility of individuals with blood group A to COVID-19, more than others, the least susceptible being O blood group individuals, but this zone of research demands to be extensively reconnoitred further.<sup>[31]</sup>

## ENVIRONMENT

Although these viruses have endured in animal or avian reservoirs for ages, precipitous introduction into the human host, on different occasions due to human encroachment into forest areas, deforestation and forest fires, which disrupt the natural habitat of bats, has led to devastating outbreaks.<sup>[8]</sup> This illustrates the significance of better understanding of human–animal interface that can help prevent such outbreaks. Such events occur frequently in China, as has been noted earlier in influenza A pandemic (H1N1), avian influenza (H5N1) and SARS pandemic, owing to their famous live wet markets, where all animal and bird species are marketed in a close proximity, countenancing them for a higher mutation rate.<sup>[8,32]</sup> These wet markets act as the principal hotspots for the emergence of these novel viruses by virtue of the continuous spillover and re-assortment occurring at both intra-species and inter-species levels. Most of these viruses emerge in winter season as higher temperature is domineering for the existence of these viruses. Though many authors have contemplated the temperature of 5°C–11°C to be apposite for transmission and rare cases have been noted in cities with colder temperature towards northern latitude, the hearsays are not established.<sup>[33,34]</sup> It is for the third time in this decade that a novel CoV has emerged intersecting the inter-species barrier. However, the present spell might prove more devastating and may herald a new pandemic, owing to better connectivity of China via snowballing trade and travel. Furthermore, overpopulation and winter season is further abetting its spread, which might prove to be catastrophic, as was noted earlier with influenza A (H1N1) pdm09 virus in 2009.

## RESERVOIR

Bats have been considered as the substantial reservoir of all coronaviruses because they harbour a diverse range of ~3204 coronaviruses, thus prone to major host switching, thereby crafting novel coronaviruses affecting human population. Two precise fluctuating events, switching and sharing, responsible for inter-genus and intra-genus transfer, respectively, account for varied spillover to human population in different regions.<sup>[32,35]</sup> The PREDICT study has revealed a strong association between the subclades and biogeography of bats, and mapping of the same unveiled homology to 2b strains of betacoronavirus.<sup>[32,35]</sup> Extensive studies have revealed that step-wise mutations in receptor-binding domain of ACE2 in SARS-CoV led to gradual spillover of the virus from bats to civets in live wet food markets and subsequently, the continuous exposure of humans to this virus led to the next inter-species crossover, enabling this virus for a stable human-to-human transmission.<sup>[8]</sup> Recent studies have revealed 96.2% homology between the bat RaTG13 CoV and SARS-CoV-2.<sup>[36]</sup> However, it is not clear if the virus directly jumped from bats to humans or any intermediate species was involved.

A very recent research has shown the maximum homology of 99% of this SARS-CoV-2 sequence to that of pangolins.



Pangolins fall in the list of ‘critically endangered species’ and are among the most trafficked animals of the world that are used as delicacy and for medicinal purposes in China and Vietnam. Owing to such a high level of identity, these can act as potential intermediate host for transmission from bats to humans [Figure 1].<sup>[37]</sup>

## PATHOGENESIS

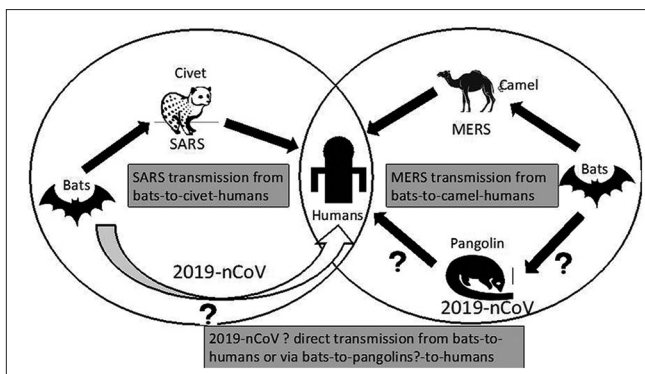
The exact pathogenesis of SARS-CoV-2 is not known, but most researchers believe that it might be similar to SARS due to sharing of the same receptor, ACE2. The virus mediates its virulence after adhesion to the host cell by means of spike (S) glycoproteins, which further acts as a second determinant because it needs to be cleaved by host cell proteases before it can execute the fusion mechanism.<sup>[38]</sup> Thereafter, it enters the host cell, transcribes and translates, generating new virions and budding into new viruses, infecting the nearby and distant cells. Host preference is determined based on this interaction. Owing to the long lineage of amino acid sequences in ACE-2 receptor, two hotspots have been recognised, regions 31 and 353, which interact with receptor-binding motif of spike glycoprotein at regions 479 and 487, respectively. It has been noted that this association is the strongest when asparagine and threonine are present at positions 479 and 487, respectively, as was noted in human SARS virus. This was found homologous to the mutations from lysine and serine to asparagine and threonine, acquired in civets over a period of time, attaining a homology of 98% with human strains. This forms the basis of intermediate host being involved in this transmission as bats had asparagine at both the substantial regions, with an identity of merely 76%. However, the homology between RaTG13 and human SARS-CoV-2 has been noted to be 97.2%, which could pave a path for direct transmission from bats to humans.<sup>[9,36,38]</sup> A recent study has refuted the recombination concept of the origin of this nCoV and proved the virus to be a non-mosaic one, being entirely distinguished in the 3’ ORF1 spanning region. It forms a separate cluster with RaTG13, distinguished from bat SARS-CoV.<sup>[39]</sup> Moreover, a wide variety of bat species have been known to reside near Hubei district in Yunnan and

nearby regions, where the switching or transmission might have been initiated.<sup>[40]</sup>

Studies have also noted the molecular dynamic interactions of nCoV with human immune system. Immunoinformatic-aided research has revealed the presence of five cytotoxic T-cell epitopes and three sequential B-cell epitopes in viral spike glycoprotein that interacts with major histocompatibility complex Class I, generating a strong immune response, and this can be further exploited in vaccine studies.<sup>[41]</sup>

## TRANSMISSION

The virus is transmitted essentially via respiratory droplets and fomites;<sup>[4]</sup> however, recent studies have unearthed the virus lurking in the gastrointestinal tract to be transmitted via faeco-oral route. The virus was found in the faeces of a patient in the USA, who presented with diarrhoea before fever.<sup>[42]</sup> Similar findings have been noted earlier in SARS pandemic, in which 10%–15% of patients had gastrointestinal symptoms. Owing to the similarity of receptors for both these viruses, SARS-CoV-2 is also expected to replicate in gastrointestinal tract, hence the name being given as ‘pneumoenteric viruses.’ However, the major risk factor remains human-to-human transmission via fomites and droplets, as has been noted in varied parts of the world where transmission via household contacts has led to a catastrophe.<sup>[43,44]</sup> The same has been noted in China in the initial peak of outbreak, where merely 31.3% had a history of travel to the implicated Wuhan market and the rest 72.3% had contact with these 31.3% of individuals.<sup>[45,46]</sup> Fomite spread is of major trepidation as the virus can outlast on surfaces for a period ranging from 2 h to 9 days. It has been noted that SARS-CoV-2 is more stable than SARS-CoV on plastic and stainless steel than on copper and cardboard. The stability kinetics on plastic for 72 h and 48 h on stainless steel was  $10^{3.7}$  to  $10^{0.6}$  TCID50 per milliliter and  $10^{3.7}$ – $10^{0.6}$ /ml, respectively. The virus was not viable on copper after 48 h and after 24 h on cardboard. The half-life of SARS-CoV and SARS-CoV-2 was analogous in aerosols, with a median estimated survival of 1.1–1.2 h, 6.8 h on plastic and 5.6 h on stainless steel. The stability of both SARS-CoV and SARS-CoV 2 was comparable, echoing the epidemiological disparities being a consequence of speckled shedding, higher viral load and distinctive transmissibility and asymptomatic patients enduring the chain of transmission.<sup>[47]</sup> Indirect transmission has also been reported from China where an asymptomatic female infected sundry person in a mall, in the absence of any direct contact, on dissimilar floors than she visited. Most of the affected individuals were females, insinuating towards restroom being a source of fomite spread, but one patient denied using restroom. Other sources of transmission could have been escalators and doorknobs, though the virus was not isolated from the same, but one of the doorknobs of her home tested positive, accentuating the indirect and fomite spread of the virus.<sup>[48]</sup> ~90% of the room sites and 60% of the toilet seats have tested positive for the virus in Singapore from an asymptomatic patient.<sup>[49]</sup> A chief impact to this unstoppable chain of transmission is by asymptomatic



**Figure 1:** Zoonotic transmission of three epidemic coronaviruses. SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, SARS-CoV-2: Severe acute respiratory syndrome coronavirus (CoV)-2

individuals, incessantly transmitting the infection.<sup>[30,50]</sup> In a study in Guangdong, China, high viral load was noted in respiratory samples of asymptomatic patients, reverberating the need of stringent quarantine.<sup>[51]</sup> Pre-symptomatic transmission has also been reported amongst two family clusters in China.<sup>[52]</sup> The same has been noted in Germany, South Korea and Italy as well.<sup>[43,44,53]</sup> South Korea, having the most comprehensive testing in the world, has reported majority of asymptomatic patients to a gamut of 30% in 20–29 years of age group, in contrast to 3.7% in the same age group in Italy.<sup>[54]</sup>

Two cases of vertical transmission have also been reported in China, where the youngest patient noted was merely 30 h after birth.<sup>[26]</sup> Though the hearsays regarding vertical transmission have grounded up, this is still less likely as the infant might have acquired the infection in the peri-natal or post-natal period, after being exposed to body fluids, secretions and environment. Moreover, recent studies from China and Iran have paraded no vertical transmission from SARS-CoV-2 mothers to their newborns.<sup>[55–60]</sup> Lately, the transmission from humans to animals has also been documented from Pomeranian dog in Hong Kong and a tigress in New York, USA.<sup>[61,62]</sup> Although the research is underway, it is of major concern as animals can play a pivotal role in the transmission dynamics of SARS-CoV-2.

The virus is spreading rampantly owing to lack of any previous herd immunity in the population. However, in view of the unknown transmission dynamics and shedding, many more cases might emerge with time. The basic reproduction number ( $R_0$ ) of the illness, defined as number of transmission events of a disease per infected person, is still cryptic. The same has been predicted to be 2.2, which is more than that of circulating influenza A pdm (H1N1), but less than SARS with a secondary attack rate of 50%–60%. Because  $R_0$  is so high, the outbreak can spread at stauncher speed across the globe; this can scarcely be a herald wave and new cases might surface again with time. Serial interval, another substantial factor frolicking an imperative role in transmission, is the time interval between one individual developing signs and symptoms of a scrupulous illness to a second person getting infected and developing the symptoms of the same, which has been illustrated to be 4 days in COVID-19, in contrast to EBOLA where it is several weeks and influenza with few days.<sup>[50,63]</sup>

Similar to SARS and MERS-CoV, this SARS-CoV-2 can prove deadlier by the so-called ‘super-spreading events’, as were noted in SARS-CoV, but their role in the present scenario is still debatable and will be unveiled with time. Nosocomial spread has also been reported, and the physician who surfaced the possibility of this as an outbreak, also succumbed to the infection. All HCWs are at a heightened risk of acquiring infection, with age, diabetes and heart disease as independent variables.<sup>[64,65]</sup>

Although the outbreak began in 2020, the same was predicted in 2018 itself, estimating a toll of 33 million lives, by billionaire philanthropist, Bill Gates, when he unveiled the lack of pandemic preparedness and the ease of spread of such

infections across the globe, based on a study conducted by the Institute of Disease Modelling.<sup>[66]</sup> Another theory given by Israeli biological warfare expert suggests this novel virus to be a deadly consequence of China’s ‘definitely covert’ research in one of the most advanced laboratories for handling such deadly zoonotic viruses that was set up lately in Wuhan. Many online videos are being circulated on social media regarding the myths linked to the emergence of this virus in China and actions taken by Chinese authorities, but these demand auxiliary ratification.<sup>[67]</sup>

## CLINICAL PRESENTATION

The patient presents with prodromal symptoms of fever, myalgia, cough and sore throat, which can become severe, and patients can flinch with shortness of breath and respiratory failure. The incubation period of illness is 14 days, with a median of 5.1 days, and ~97.5% of the patients develop symptoms within 11.5 days.<sup>[63]</sup> Few of the patients also present with diarrhoea.<sup>[42]</sup> Nearly 51% of the patients presented with dyspnoea, 37% with acute respiratory distress and 39% of the patients required admission to the intensive care unit (ICU).<sup>[25]</sup> Lately, anosmia has been reported from a large cohort of patients who have tested positive for the disease. ~30% of the patients presented with post-COVID-19 anosmia in South Korea.<sup>[68]</sup> Although post-viral anosmia is usual, accounting for 40% of the humdrum cases, anosmia after COVID-19 is supplementary and serves as a telltale for the infection, following which many countries have advised their citizens to self-quarantine themselves discerning anosmia.<sup>[69]</sup> Complications such as pneumonia, cardiac injury, respiratory failure and acute respiratory distress syndrome have been reported from China. A study conducted on 201 patients in Wuhan has predicted the parameters for severe acute respiratory distress syndrome (ARDS) in COVID-19 patients. The authors established the mean age as 51 years, with two-thirds of the patients being males. Almost three-fourths presented with fever and cough; more than one-thirds with fever and dyspnoea; and one-third with fever along with fatigue, myalgia and headache. Nearly 6.5% of the patients had fever and out of all these, 71.6% were discharged without showing any complications. Of 41.8% of the patients developing ARDS, more than half were deceased. The factors that were encountered more in this group of patients include dyspnoea in >59.5%, hypertension in 27.4% and diabetes in 19% and treatment with methylprednisolone. The risk factors that were statistically significant in the progression of ARDS to mortality include older age, neutrophilia, organ and coagulation dysfunction with raised lactate dehydrogenase and D-dimers. Patients with a fever of  $\geq 39^\circ\text{C}$  and methylprednisolone had more chances of developing ARDS, without increasing the mortality.<sup>[70]</sup> Computed tomography of 56.4% of the patients showed ground-glass opacities and bilateral patchy shadows in 51.8% of patients.<sup>[46]</sup> A late complication in the form of rhabdomyolysis has also been reported in a 60-year-old male patient, who presented with pain and weakness of the lower limbs.<sup>[71]</sup>

A CFR of 4.2% has been documented in China,<sup>[25]</sup> but varies from region to region as has been noted in Italy, which is much

less than that of SARS and MERS, but the number of cases affected precedes both these infections. Many researchers have studied the predictors of mortality and have noted increased levels of ferritin, an acute-phase reactant that is produced in larger quantities by hyper-stimulated immune system and interleukin (IL)-6, a pro-inflammatory cytokine,<sup>[72,73]</sup> elevated inflammatory indicators in blood; age; comorbidities and secondary infections to be playing a significant role in determining the fatality. On a closer sight, almost all the modifiable parameters are indirectly linked to a virus-induced cytokine storm.<sup>[73]</sup> A study of 140 patients in Wuhan, China, divulged eosinopenia with lymphopenia as other significant predictors of mortality.<sup>[74]</sup>

## RESPONSE OF WORLD HEALTH ORGANIZATION AND INTERNATIONAL AGENCIES TO THE SITUATION

The World Health Organization (WHO) has vindicated the chances of spread to more countries. Since more than 28 countries have been affected and the rate was doubling frequently, the International Health Regulations committee declared this as a 'Public Health Emergency of International Concern (PHEIC)' on 30 January 2020 after human-to-human transmission was confirmed in the USA.<sup>[4,75]</sup> The WHO has announced Level 3 travel restrictions and has advised to gear up the surveillance to limit import and export of this virus. Non-essential travel should be avoided, and the WHO urges caution in the event of travel to the hotspot region and lately, these restrictions have been escalated, admonishing the travel by restricting entry and rescinding visas temporarily to ground zero. However, the USA has proclaimed 'Level 4' restrictions implicating 'Do not travel', with a very delimited entry for everyone travelling from China in the past 2 weeks and a direct denial to foreign nationals, apart from the immediate family of US citizens, who will be quarantined for 2 weeks. Many countries including the Philippines, Bangladesh, Sri Lanka, Malaysia, Mozambique, Russia, Singapore and Vietnam have suspended airlines and stopped issuing visas to Chinese travellers, and many of the nations are under lockdown.<sup>[4]</sup>

Because the outbreak could have become apocalyptic in view of the Lunar New Year, when mass population movement was envisaged, the Government of China cancelled all the celebrations and has quarantined seven major cities to contain its spread. Wuhan, which is ~3000 miles from Beijing, is densely populated, is an educational and business hub and is under a lockdown state since January 2020. China has built a new emergency hospital within merely 10 days, to cope up with the rising number of patients and a batch of fifty patients has already been admitted there, who were transported via negative-pressure isolation ambulances. Robots are being used in China to provide food, medication and basic amenities to confirmed cases so that direct contact and transmission can be belittled. Robots have also been employed on roads to remind citizens, who are not taking the recommended precautions, and also at airports for thermal screening and awareness purpose.

The same has been trailed in Kerala also to generate awareness, distribute masks and sanitizers to public.<sup>[76,77]</sup>

## INDIA'S PREPAREDNESS TO CONSTRAINT SEVERE ACUTE RESPIRATORY SYNDROME-CORONAVIRUS-2

India has responded swiftly to the emergency situation, and *Air India* flights have evacuated Indian nationals from Wuhan and many others across the globe, and arrangements have been made for screening and quarantining these rescued students. Quarantine and travel ban are old tools but the primary mode of defence in the paradigm of spread of a novel virus with a high transmissibility. The responsibility for the same has been given to Armed Forces and Indo-Tibetan border police, and quarantine facility has been established at Manesar, in Southwest and ITBP Chhawla camp, near New Delhi, which are designated for monitoring and isolation of the evacuated people for 2 weeks. The facility is divided into different sectors, each one with a maximum capacity to accommodate fifty students. Each sector has several barracks, with no mingling of intersectoral or interbarrack students. The cases are to be categorised under the following three categories: suspect cases, close contacts and non-contacts. The suspect cases include the symptomatic cases with a travel history to China and these will be directly referred to the hospitals, while the close contacts and non-contacts will be transferred in earmarked vehicles to the quarantined facility and will be monitored for a period of 2 weeks. However, if an individual is found infected at any point, that affected case will be transferred to an isolation ward at Base Hospital in Delhi Cantonment.<sup>[78]</sup> All the quarantined students have tested negative for SARS-CoV-2 by All India Institute of Medical Sciences (AIIMS), Delhi. All the cases with a history of travel to foreign countries have been quarantined at home.<sup>[78]</sup> The home-quarantined individuals are being stamped with indelible ink on their hand, to ensure their restriction in movement.<sup>[79]</sup> The houses under quarantine are being marked and quarantine posters are displayed in front of these houses to adjourn the in-and-out movement from the same.<sup>[80]</sup> An extensive contact tracing, the second most significant phase of this battle, by epidemiologists of all the positive cases, is being carried out so that no person who came in contact with the infected individual is left untested and unaware.<sup>[81]</sup> The diagnostic criteria have been expanded to curtail any loophole in the diagnosis of cases. All the hospitals have been advised to defer the outpatient services, with effective functioning of all the emergency and coronavirus-screening facilities. Drills for COVID-19 preparedness need to be conducted periodically. The healthcare facilities should be well equipped with personal protective equipment (PPE), three-layered, and N95 masks, sanitizers, negative pressure rooms and ventilators to deal with the deadly pandemics with war-room thinking. In view of the dwindling availability of ventilators in India, 40,000 ventilators for a colossal population of 1.3 billion, the Government has ordered the procurement of more ventilators to be prepared for the fight against SARS-CoV-2, if the cases continue to emerge.<sup>[82,83]</sup>



As of 24 March 2020, 519 cases of laboratory-confirmed SARS-CoV-2 have been reported across the country, with maximum number of cases, 95 from Kerala, followed by 89 from Maharashtra and 35 from Telangana with ten deaths. Chandigarh has confirmed seven cases of COVID-19 till date. A total of 18,383 samples from 17,493 individuals have been tested till date. As the cases have swept across the nation, the country is under stringent lockdown. The State governments are well prepared for tackling the situation and are working on the protocols issued by the Indian Council of Medical Research (ICMR), Integrated Disease Surveillance Programme and WHO. The ICMR is working in collaboration with National Institute of Virology (NIV), Pune, to combat the rising trend and is mentoring all the laboratories, real-time reporting, quality assurance and strategy formulation. In India, over the last few years, the Department of Health Research, Government of India, had established various Virus Research Diagnostic Laboratories (VRDLs) throughout the country, which are routinely offering diagnostic assistance for influenza, and their capacity is being built up to handle impending viral threats like the current SARS-CoV-2.<sup>[78]</sup> A total of 119 laboratories along with 16 private laboratories have been designated by the ICMR for COVID-19 testing.<sup>[84]</sup> The ICMR has also equipped additional Council of Scientific and Industrial Research, Department of Biotechnology and Defence Research, Development Organisation laboratories for diagnostic testing of COVID-19 in government sector and is in a process to enable private laboratories accredited by the National Accreditation Board for Testing and Calibration Laboratories to be prepared for future endeavours if the cases note an upsurge.<sup>[85]</sup> Presently, the whole of the India is under lockdown for 21 days from 24 March 2020, to 14 April 2020.<sup>[86]</sup> India is utilising the isolation and quarantine strategy to maintain the social distancing and to prevent the further spread of the virus across space and time. Quarantine is separation of persons who have been exposed to the infection, while isolation is separation of persons who are already known to be infected.<sup>[87]</sup> In spite of the strict efforts, the Muslim missionary movement, the Tablighi Jamaat, in New Delhi's Nizamuddin area, has served as the principal spreader event for the upsurge in the peak of COVID-19 cases, preventing the expected flattening of the curve.<sup>[88]</sup> The country is under disinfection and sanitation drive. Spray tunnels with contact period of 5 s with sodium hypochlorite are being installed at many places.<sup>[89]</sup> However, the use of these tunnels is still debatable as spray on humans leads to irritation of skin and mucous membranes. The drive-through and mobile booths, based on the South Korean model, have been employed at varied regions in the country to augment the diagnostic testing.<sup>[90]</sup> The Prime Minister of India conducted a meeting of all South Asian Association for Regional Cooperation members to discuss the gargantuan threat and to raise the funds for COVID-19 illness.<sup>[91]</sup> The government has also invoked disaster management and Section 2 of epidemic act that allow the state and centre to detain any person or vessel, which might serve as a potential threat to others, pertaining the blowout of illness.<sup>[92]</sup> India has

recently supported Bangladesh by providing masks and head covers to fight the deadly virus.<sup>[93]</sup> In addition to the technical measures, the Prime Minister of India has also tried to unite all the citizens of the country by expressing the gratitude to front liners, HCWs, supply chain workers, sanitation workers and police and by encouraging one and all to stay indoors by adopting two-step procedure: resolve and restrain.<sup>[94]</sup>

## DIAGNOSIS

### Case definitions

Case definitions for the diagnosis of suspected, probable and confirmed cases have been outlined. Since the developments are constantly fruiting, these keep on evolving dynamically with time.

#### *Suspect case*

Any person who satisfies both clinical and epidemiological benchmarks, without laboratory confirmation.

Clinical criteria – Patients with fever or cough or breathlessness.

Epidemiological criteria – Any travel history to China or country with local transmission; in the past 14 days.

- OR a HCW
- OR any individual with acute respiratory illness and a history of contact with a confirmed case within 14 days erstwhile the onset of symptoms
- OR an individual with acute respiratory illness, who requires hospitalisation without other explicable aetiology
- OR a patient with inconclusive results
- OR asymptomatic high-risk or direct contacts of confirmed case, to be tested between days 5 and 14 of contact.

#### *Confirmed case*

A person who tests positive for SARS-CoV-2, regardless of the presentation.

#### *Contact*

A person who has been providing direct care to patients without PPE or has been staying in close proximity of patients or has travelled together in close proximity (1 m) with a person who tested positive later on.

The Centers for Disease Control and Prevention has catalogued contacts into two groups: high-risk and low-risk contacts.

#### *High-risk contact*

A person who has been in contact of body fluids of positive patient or had a direct contact with his/her body, including physical examination without PPE, or has touched clothing, dishes, linen of the patient or lives in the same household or in close vicinity (within 3 feet) or has travelled within close vicinity (within 3 feet) with a symptomatic patient, who tested positive later on or being with patient face to face for 15 min and in the same room for 2 h.

#### *Low-risk contact*

A person who has shared the same space for <15 min or



distance more than 3 feet or has travelled together, without having a high-risk exposure.<sup>[95]</sup>

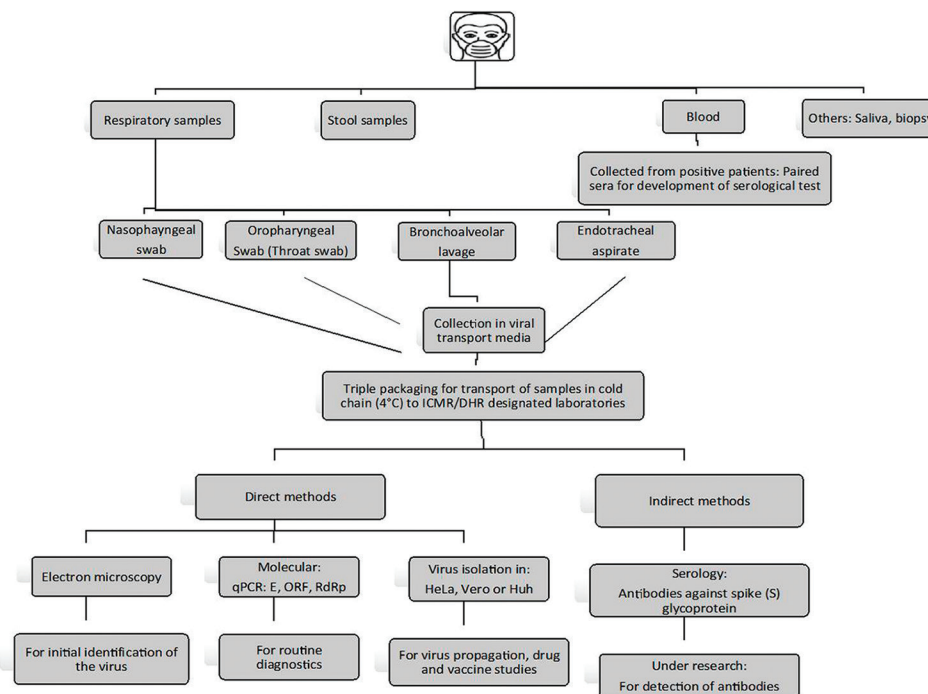
The current recommendations of testing by the ICMR include all asymptomatic individuals with a travel history of international travel within the last 14 days (testing after being symptomatic), symptomatic HCWs, symptomatic contacts of positive cases, all hospitalised patients with severe acute respiratory illness and asymptomatic direct as well as high-risk contacts of a positive confirmed case.<sup>[96]</sup> The ICMR has formulated five different categories for the same that include: Category 1: All symptomatic international travellers within the last 14 days. Category 2: All symptomatic contacts of laboratory-confirmed case. Category 3: All symptomatic HCWs. Category 4: All hospitalised subacute respiratory illness (SARI) patients. Category 5a: All asymptomatic direct and high-risk contacts of the confirmed case: Family members and Category 5b: All asymptomatic HCWs, Category 6: Symptomatic influenza-like illness (ILI) patient in hospital/MoHFW identified clusters. Pregnant women inhabiting in containment zones or migration clusters from hotspot regions, presenting with labour or due in five days ought to be tested, irrespective of symptoms. who came in contact with the confirmed case without adequate PPE.<sup>[85]</sup> More stringent categories need to be devised in conduit of influenza A pandemic (H1N1) depending on the severity of illness to attain a more rational usage of PPE and other resources. The Government of India has categorized all the districts into four zones: Red (with more than 100 confirmed cases), orange (Cases between 20-100), yellow (less than 20 cases) and green (with no cases). The Infectious Disease Society of America has proposed a four-tiered approach for the diagnosis of COVID-19, in view of the rising numbers and scarce facilities. Tier 1 includes testing of critically ill patients with unexplainable symptoms; patients with respiratory symptoms having a history of contact or travel; patients with respiratory symptoms who are immunocompromised or are elderly with comorbid conditions and patients who are essential service workers. Tier 2 encompasses non-ICU patients and residents of long-term care facilities presenting with the symptoms. Tier 3 includes outpatient department patients, who fit in for influenza testing or those with specific comorbid conditions such as chronic obstructive pulmonary disease, cardiovascular problems, diabetes or pregnant females or children with comorbidities. Tier 4 has those community individuals who are being monitored for surveillance and data collection for COVID-19 prevalence.<sup>[97]</sup> The expansive and well-organised diagnostic capability at a large scale is the key to early diagnose and control the cases. The South Korea model needs to be emulated, where they tested 270,000 samples with 5200 per million, which is 60% of their total population by starting drive-through testing centres.<sup>[44,54]</sup>

### Sample collection

In individuals with travel history to other parts of China, it was recommended to collect samples from symptomatic cases only, during the initial wave of COVID 19 in China. However, sputum, serum and stool are also obliging, especially in patients with a history of diarrhoea. For individuals with

a travel history to other parts of China, samples are to be taken from symptomatic cases only.<sup>[98]</sup> Urine samples can also be tested to exclude other cryptic modes of transmission.<sup>[2]</sup> Samples from both upper and lower respiratory tract are accepted, while the latter are preferred. Nasopharyngeal swab, nasal swab, oropharyngeal swab, sputum, bronchoalveolar lavage, endotracheal aspirates or wash and tissue biopsy are the preferred samples. A study conducted in China has divulged a higher viral load from nasal swabs more than the throat swabs.<sup>[51]</sup> Another study by Tang *et al.* discovered the significance of testing the stool samples. A 10-year-old asymptomatic male child, who had contact with two confirmed cases, was tested for SARS-CoV using respiratory samples that tested indeterminate twice, and the result was conclusively established after the stool sample tested positive.<sup>[99]</sup> Lower sensitivity of upper respiratory samples has also been reported in case of co-infection, contributing to false-negative results.<sup>[100]</sup> A study conducted on varied clinical samples for uncovering virus in China has divulged the sensitivity of commonly used nasopharyngeal swab to be as low as 32%, nasal swab as 63%, sputum as 72%, bronchoalveolar lavage as 93%, stool as 29% and blood with a sensitivity of 1%.<sup>[101]</sup> Few cases of viraemia have also been reported across the world.<sup>[101,102]</sup> The virus has not been detected in urine till date. High viral load has been detected in nasal swabs more than pharyngeal swabs, with the load being maximum just after the onset of symptoms, with viral shedding trailing the same pattern as influenza. A same rate of viral load has been detected in asymptomatic patients, making them a colonel trajectory for transmission.<sup>[103]</sup> Respiratory samples should be collected in viral transport medium, containing antibiotics and antifungals, and should be transported in cold chain with triple packaging [Figure 2]. Case sheets and identification details with proper labelling of the sample along with sender's and receivers' details, should be placed in plastic bags and pasted outside the tertiary container.<sup>[98]</sup> All the procedures from sample collection to packaging should be done taking stringent contact precautions, using PPE with eye protection, three-layered surgical mask (the use of N95 mask should be restricted to sample collection and in patient care), disposable gown, gloves and shoe covers. This should preferably be performed in a negative-pressure isolation room and the sample should be processed using calibrated Class II biosafety cabinets.

The collected samples should be referred to the designated laboratories assigned by the ICMR to test for the novel virus, with the apex institute being NIV, Pune. Lately, the ICMR has assigned one centre per state and has issued a list of state nodal VRDLs for testing of nCoV using real-time polymerase chain reaction (PCR), along with guidance document for the same. All the individuals with a travel history to Wuhan after 15 January 2020, should be tested for SARS-CoV-2, irrespective of symptoms. For patients with a travel history to the rest of China, samples should be tested only from symptomatic patients. Till the receipt of primers and positive control, these state VRDLs will send the suspected samples



**Figure 2:** Diagnostic algorithm for severe acute respiratory syndrome-coronavirus-2. ICMR: Indian Council of Medical Research, DHR: Department of Health Research, qPCR: Real-time polymerase chain reaction, E: Envelope protein, ORF: Open reading frame, RdRp: RNA-dependent RNA polymerase

to NIV, Pune, after triple packaging. After validating the first reaction using these reagents, results will be verified by NIV, Pune, and afterwards, the testing of suspected samples would be initiated. All positive samples and representative negative samples need to be shipped to NIV, Pune, on a real-time basis for quality check. Blood samples from positive cases will also be sent to the same laboratory for confirmation and paired sera for the development of serological test. For any positive case, a convalescent sample should be repeated after 2 weeks. All the results should be kept confidential and disclosed only to NIV, Pune, and the concerned authorities. To rule out the community transmission, the ICMR is also testing samples of patients with severe acute respiratory illness, other than COVID-19, and all the samples have tested negative, ruling out the propensity of community spread in India till date, though some of the reports claim that India is currently in between Stages 2 and 3.<sup>[104]</sup>

### Diagnostic testing

Currently, the diagnostics are utilising real-time PCR for detection of the virus. Earlier, pan CoV marker genes were being used to screen the positive samples, followed by sequencing for the identification of SARS-CoV-2. Presently, many platforms for testing SARS-CoV-2 are available: in-house National Institute of Virology (NIV) assay in which E gene is being targeted in screening tests, while RdRp and ORF genes are the targets for confirmatory testing; Roche COBAS-6800/8800 targeting E and RdRp gene; TaqPath ABI targeting S, N and orf-1 ab genes; Cepheid GeneXpert targeting N2 and E gene and Truenat for screening. The ICMR/NIV has also validated other commercial kits such as Altona diagnostics (RealStar Altona Diagnostics GmbH, Hamburg, Germany) targeting

E and S genes; MY LAB Patho detect kit (make-in-India product); KILPEST (TRUPCR Blackbio Biotech, Bhopal) targeting E, RdRp and N genes; Seegene (Allplex) targeting E, RdRp and N genes and SD Biosensor kits targeting E and RdRp ORF 1 ab genes.<sup>[85]</sup> Of all these platforms, Truenat, another make-in-India product that has been widely used for the diagnosis of tuberculosis, is recommended only for screening of COVID-19, whereas TaqPath platform is more favourable because it incorporates both screening and confirmatory tests in a single step. High-throughput platforms such as Roche 6800 have been phased out in NCDC, Delhi and National Institute of Biologicals and Regional Medical Research Center, Bhubaneswar. The Food and Drug Administration (FDA) has also approved a real-time PCR-based diagnostic test on an emergency basis, for the detection of SARS-CoV-2. It incorporates four targets, N1, N2, N3 and RP, out of which N1, N2 and N3 along with RP gene should be present for a sample to be reported as positive and in samples where only one or two targets are present, test is reported as inconclusive. In scenarios where RP is negative, the test is reported invalid and needs to be repeated. In spite of numerous testing platforms available, nevertheless, negative test does not exclude infection. In an era of next-generation sequencing and bioinformatics, hastened attempts to develop a rapid serological test targeting ORF1 ab, N and E genes on a fast track mode is the need of the hour. Lately, a healthcare company has launched a new molecular Primerdesign test (genesig SARS-CoV-2) for the rapid diagnosis of 2019-nCoV. For further evaluation of such samples, an in-house multiplex PCR to exclude common respiratory pathogens can also be used in view of cost restraints

to screen the patients for other respiratory viruses, which are in circulation owing to the winter season in India.<sup>[105]</sup>

Cepheid, known for developing point-of-care tests for tuberculosis, *Trichomonas vaginalis*, *Clostridium difficile*, EBOLA and others, has also developed a rapid diagnostic test for the detection of SARS-CoV-2, and the test is both FDA and ICMR approved under emergency use authorization (EUA). The test is named as Xpert Xpress SARS-CoV-2 and is based on the principle of RT-PCR for qualitative detection of the nucleic acid, targeting N2 and E genes. If both the targets are present, it is considered as a positive test. If N2 gene is present and E gene is absent, the test is still considered to be positive, however, in absence of N2 gene and presence of E gene, result is considered as presumptive positive. Nasopharyngeal swab, nasal wash and aspirate are the recommended samples. The hands-on time for the same is <1 min and the turnaround time is 45 min, thereby lining I for the front line point-of-care test.<sup>[106,107]</sup> Another test that has been approved by the FDA under EUA is RT-based Quidel's test of Lyra.<sup>[108]</sup> Currently, other kits including the one designed by IIT, New Delhi, is under fast-track approval by the government. The IIT, Delhi COVID kit is a probe-free detection assay designed for targeting unique regions of SARS-CoV-2, which will be easier and cheaper with a lesser turnaround time.<sup>[84,109]</sup> These commercial kits are of prodigious succour in diagnosis as it befits easy to troubleshoot and validate the results. Recently, the ICMR has licensed antibody kits for diagnosis in blood to bridge the rising demand and testing of COVID-19. The IgM/IgG kit detects antibodies against spike glycoprotein of SARS-CoV-2 in blood, however, being an antibody detection test.<sup>[85,110,111]</sup> It has been noted that the antibodies begin to be form after 10 days of infection and seroconversion is noted within 3 weeks.<sup>[112]</sup> Detection of antigen is also being developed, and many kits have already been commercialised for research and surveillance use.<sup>[113]</sup> CRISPR technology is also being exploited to the extreme for the development of diagnostic tests.<sup>[114]</sup> There is an exigent necessity to ascertain the clinical criteria, along with the usage of biomarkers for predicting the infection. Zhou *et al.* have divulged the role of ferritin, C-reactive protein and procalcitonin in predicting poor outcome in very severe COVID-19 patients, owing to secondary bacterial infections, however, additional research is stipulated in this field.<sup>[115]</sup> It is noteworthy that Hunan, China, has been experiencing an outbreak of highly pathogenic avian influenza virus of type A of subtype H5N1 at Shaoyang farm where 4500 chickens of total 7850 have died of this highly pathogenic strain. Nearly 18,000 chickens throughout the province have been culled afterwards, owing to the potential of avian influenza virus to mutate rapidly, with the potential of spread to humans.<sup>[116]</sup> A case of co-infection of COVID-19 with influenza A virus has also been reported that deferred the early diagnosis of the case, owing to co-infection as well as lower sensitivity of the upper respiratory tract samples.<sup>[100]</sup> Hence, human surveillance for other pathogenic viruses is also desirable at the same time as screening for SARS-CoV-2 to identify animal-to-human transmission.

In India, smartphones and Internet facility is available with one and all, which can be commendably exploited to disseminate easily adaptable management strategies. The

innovative studies by Radin *et al.*<sup>[117]</sup> and Cecile *et al.* have successfully disclosed the utility of fitbit wearable devices in anticipating influenza-like illness,<sup>[118]</sup> which can be reproduced in the present scenario as well by the use of such smart fitness devices. Moreover, there is an imperative prerequisite to transform the testing and reporting drudgery to software-based, paperless platform.

## MANAGEMENT

The confirmed cases are being managed using antivirals to combat other agents exacerbating respiratory illness, intravenous infusions and oxygen therapy to maintain positive end-expiratory pressure extracorporeal life support and neuromuscular blockers in case of ARDS. Corticosteroids and hypotonic crystalloids are not recommended for use in therapy. Dedicated COVID hospitals have been built up to combat the war with deadly virus. Such 1200-bedded hospitals have been built up in Ahmedabad and Chandigarh and ~2500 coaches in trains have been converted into isolation cabins.<sup>[119-121]</sup> Many researchers have propositioned the deteriorating effects of ibuprofen in the management of COVID-19 because ibuprofen upregulates the ACE receptors, thereby making the individual more susceptible to infection by SARS-CoV-2, owing to its adherence to ACE receptors. The same footholds true for thiazolidinone group of drugs.<sup>[122]</sup> The WHO and European Medicines Agency (EMA) have directed the use of ibuprofen in lower doses for shorter duration, but has not bolstered against the use of ibuprofen in view of the derisory evidence and absence of large epidemiological studies.<sup>[123,124]</sup> No specific anti-CoV drugs are currently available. As per some of the claims, one of the patients in Wuhan has been cured after the use of nelfinavir, a protease inhibitor used in the treatment of human immunodeficiency virus (HIV), but these claims have no firm basis.<sup>[125]</sup> Other drugs that are being second-handed and have shown therapeutic success in Thailand include cocktail of anti-HIV drugs in combination with anti-influenza drugs; lopinavir, ritonavir, plus oseltamivir. The same drugs were used in SARS epidemic and have proved to be of immense succour in the management of such cases.<sup>[126]</sup> Lopinavir is a 3CL protease inhibitor with a modest action against the virus, whereas ritonavir augments its bioavailability, complementing the immunomodulatory activity of the combination by inhibiting the interferon (IFN)-beta1 $\beta$ , as was eminent during the MERS outbreak. The combination is effortlessly available and can be instantaneously prescribed. However, recent studies have divulged no added advantage for all the patients, exhibiting zero benefit at primary end point, in the form of clinical improvement while an intriguing benefit was comprehended, in the form of declined mortality, at the secondary end-point.<sup>[127]</sup> Another randomised controlled trial in adult COVID-19 patients paraded a median time lag of improvement of merely 1 day in patients on treatment with this combination when compared to the standard care, while the viral load in both the study arms was similar. On the contrary, the gastrointestinal adverse effects were more commonly



encountered in the combination study group while the severe adverse events were more in the standard arm. Moreover, the combination treatment had to be worn out prematurely in 13.8% of the patients.<sup>[128]</sup> Clinical trials using darunavir and cobicistat are also underway. Remdesivir, a novel nucleotide analogue discovered for the treatment of Ebola and Marburg, is also being tried for the management of severe cases, and has entered Phase III trials.<sup>[12,129-132]</sup> Remdesivir acts on NSP12 even when ExoN is intact.<sup>[133]</sup> The drug has shown potential success in the treatment of MERS, more effectively than other protease inhibitors and Ebola to a lesser extent, and has successfully treated many COVID-19 patients as well, including the first case in the USA.<sup>[42,130]</sup> Recently, Wang *et al.* have conducted a study determining the cytotoxicity, virus yield and infection rate of ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir and favipiravir. The authors have shown remdesivir and chloroquine to be highly effective against SARS-CoV-2, and this has entered clinical trials for the same.<sup>[12]</sup>

Sarilumab, a human monoclonal antibody and a known drug for the management of rheumatoid arthritis, is currently being repurposed for the treatment of SARS-CoV-2, outstanding its knack to inhibit IL-6 pathway by binding and blocking the receptors. It has been resurfaced in the management of COVID-19 because IL-6 is a potent cytokine, both innate and acquired immunity armour, which induces hyper-inflammation in lungs, thereby deteriorating the disease. Sarilumab prevents this inflammatory cascade in the body, stabilising the condition of affected patients. Tocilizumab is also one of such potent IL-6 inhibitors that helps reduce IL-6 as well as IL-1 $\beta$  levels. This drug has been given in 19 patients, who responded well with 13.5 days' duration of hospital stay. IL-37 and IL-38 are other immunosuppressive cytokines that act on mTOR, further increasing adenosine monophosphate (AMP) and inhibiting the MyD88 pathway that reduces the pro-inflammatory cytokines, preventing further damage.<sup>[134]</sup> Anakinra, an IL-1 blocker, can also be used to block the overstimulation of immune system without exhibiting adverse effects.<sup>[72]</sup> Emapalumab, an anti-IFN gamma antibody has also been proposed as a potential candidate to counter the hyperinflammatory syndrome, and both anakinra and emapalumab have been enrolled for clinical trial by Swedish Orphan Biovitrum AB (SOBI) that will be started soon.<sup>[135]</sup>

Chloroquine and hydroxychloroquine, anti-malarial and anti-rheumatoid, anti-SLE and anti-porphyrin drugs, have been noted to be effective as an oral alternative to remdesivir against SARS-CoV-2. The mechanism involved is contemplated to be pH-dependent inhibition of viral replication. An auxiliary advantage is immunomodulatory action by inhibition of IL-6 and tumour necrosis factor- $\alpha$ , with a novel action as an autophagy inhibitor, interfering with viral replication. The drug acts at both entry and exit points of viral entry by inhibiting glycosylation of receptors, as has been documented in Vero-E6 cell lines.<sup>[45,136-138]</sup> The ICMR has recommended the use of this drug in asymptomatic HCWs who are directly

involved in the care of suspected or confirmed cases and asymptomatic household contacts of laboratory-confirmed cases. The dosage advised in both the cases is 400 mg twice a day on day 1, followed by 400 mg once weekly with meals. However, the duration in the former will be 7 weeks and 3 weeks in the latter. The contraindications to this are age <15 years, retinopathy and known hypersensitivity to 4-aminoquinolone compounds.<sup>[96]</sup> Another antiparasitic drug that has been repurposed for use against the noxious virus is ivermectin. Ivermectin inhibits the nuclear transport system of the virus leading to ~5000-fold reduction in viral numbers in Vero/hSLAM cell culture. The FDA has approved the drug for use in COVID-19 patients owing to its safety profile and easy availability as the drug is included under the WHO list of essential medicines.<sup>[139]</sup>

M<sup>pro</sup> has been identified as a potential drug target, based on binding free energy, homology modelling and molecular docking, and is currently under research.<sup>[125]</sup> Insights into spike (S) glycoprotein have revealed that it is mandatory for the entry into host cell and can serve as a therapeutic target as well, and the same has been noted with TMPRSS2.<sup>[140]</sup> Another treatment option to curb the infection is usage of ACE2 inhibitors such as telmisartan and losartan as these do not have cough as adverse effect, unlike other ACE inhibitors.<sup>[141,142]</sup> Few researchers have suggested combination of ACE2 inhibitors with Fc component to have a triple action, by inhibiting the receptors along with enhancing the immune system via Fc and by reducing the ACE levels in lungs, thereby reducing the inflammation.<sup>[142]</sup> However, there are concerns against the use of these drugs in the management of COVID-19 as these drugs can upregulate the ACE receptors after prolonged usage.<sup>[143]</sup> Concerns have also been raised with regard to their deferral in suspected patients, however, the cardiac society has advised to continue these drugs and has reported these to be protective in animal models.<sup>[144]</sup> Baricitinib is also a potential target that acts upon AP2-associated protein kinase 1 (AAK1), which plays a significant role in endocytosis necessary for entry of this virus. It is preferred over other AAK1 inhibitors owing to few adverse effects and a co-action on cyclin G-associated kinase and Janus kinase signal transducer and activator of transcription protein (JAK-Stat) pathway.<sup>[145]</sup> Other drug targets such as RdRp and CL<sup>pro</sup> can also be used to curb the spread of virus.<sup>[146]</sup> Plasma therapy for limiting complications in critically-ill patients is also underway, in which convalescent plasma from recovered COVID-19 patients is being used. The Drug Controller General India has also approved the use of these drugs in severe cases, and all the authorities are working for the rapid approval of diagnostic tests, drugs and vaccines at a fast track mode. Owing to escalation in the number of cases worldwide and the unavailability of any specific targeted therapy, The WHO has initiated SOLIDARITY trial across the globe with an unprecedented and coordinated effort to assemble robust data during the pandemic by use of simple steps. The physician from any nation needs to add all the details of positive case, any associated comorbidity and the available



drugs in the hospital. The WHO will then, further randomise the patient and allocate it to either of the following four groups: remdesivir group, lopinavir/ritonavir group, lopinavir/ritonavir group with IFN-beta and chloroquine group.<sup>[147]</sup> Another such trial has been launched in Europe also, the DISCOVERY trial, in which patients will be randomly allocated into the following five groups: standard of care, standard of care plus remdesivir, standard of care plus lopinavir/ritonavir, standard of care plus lopinavir/ritonavir plus IFN-beta and standard of care plus hydroxychloroquine.<sup>[148]</sup> Though the drug of choice is not available yet, therapeutic success with these drugs might act as 'light in the tunnel' for the management of these cases.

## PREVENTION

The virus is amenable to simple preventive strategies including social distancing and stringent adherence to hand hygiene and cough etiquettes at all levels, beginning from schools and home to industries and healthcare facilities. Social distancing with a minimum of 6 feet distance is imperative to curb the transmission from one to all. Though use of masks is considered substantial in domineering the respiratory route of spread, hand hygiene is the 'need of the hour'. Owing to the prospect of faeco-oral and other cryptic modes of transmission, hand hygiene plays an imperative role to contain this outbreak.

### Risk stratification

The WHO has classified the affected cases into the following four risk groups: high, intermediate, low and no risk.

- a. High risk: This includes the individuals living in the same household or being healthcare provider or partner of the confirmed case or to a person having a history of travel to the hotspot region. Such cases are to be dealt immediately and are quarantined
- b. Medium risk: Individuals in close contact with a symptomatic or laboratory-confirmed case, but less than the high-risk exposure. These strata incorporate those patients who had contact but using the recommended precautions, in aircraft, outdoor or at home. Isolation and monitoring is recommended in these cases
- c. Low risk: Individuals being in close contact, but not meeting the above criteria. Travel to crowded places should be avoided and medical advice should be sought in case patient develops any symptoms
- d. No identifiable risk: Individuals having very brief contact, such as walking by the confirmed case or being in same room for a very short span of time. No restrictions are required.<sup>[149]</sup>

### Screening at airports and seaports

To avoid the skyrocketing rise of cases, many countries have initiated screening and isolation at airports. After the WHO declared this a PHEIC on 31 January 2020, nations across the globe are restricting the import and export, along with carrying out the evacuation of their respective citizens from the epicentre, Wuhan. Many worldwide airlines have restricted their flights to Wuhan and adjoining regions in China. India has issued a travel advisory for people visiting China and has

stepped up surveillance at international airports as well as seaports, using thermal sensors. Anyone with a travel history to China on and after 15 January 2020, should be quarantined for a period of 14 days.<sup>[150]</sup> Presently, the nation is under second phase of lockdown till May 3, 2020; after the first phase of lockdown which culminated on April 14, 2020.<sup>[151]</sup>

### Travel restrictions

The WHO has announced Level 2 restrictions with advice to avoid 'non-essential travel' to the epicentre, admonishing the travel by restricting entry and rescinding visas temporarily to ground zero. Initially in India, a total of 22 airports and six seaports were under a continuous surveillance, which was extended to a complete deferral of all international flights. The e-visas stand temporarily suspended. Those having compelling reasons for the travel will need to contact Indian embassy or consultancy offices in Shanghai or Guangzhou for the same.<sup>[150]</sup> For latest updates, country-specific advisories must be checked as due to rampant spread, these are being monitored and advised on a real-time basis.

### Preparedness at healthcare worker level

Adequate preparedness in healthcare facilities is desirable to handle such emergency outbreak scenarios. Rapid response teams comprising physicians, microbiologists, epidemiologists, infection control officer and administrative officer along with field workers, should be framed in all the primary institutions, and staff should be trained at periodic intervals for donning, doffing, spill and needle stick injury management and mock-drills should be conducted. Capacity building of all HCWs should be done for outbreak preparedness. Adequate PPE should be stock piled and handy as purchase procedures after the outbreak sparks are tedious and time-consuming. The Ministry of Health and Family Welfare has issued guidelines for rationale use of PPE at all the strata, from pre-hospital services to in-patient services to in-field testing. As per the guidelines for point-of-entry, health desk, immigration, airport security, temperature recording staff is at a low risk, while holding, isolation area and sanitary staff are at moderate risk and those dealing with severely ill patients in isolation facility are at a high risk. Comparably, for hospitals, triage, screening, registration, temperature recording, waiting section staff, doctor's chamber and sanitary staff are at moderate risk and the visitors with children and elderly are at a low risk. For inpatients, those dealing with ICU patients are at a high risk and the rest are at moderate risk. For pre-hospital services, the driver is at low risk, while transport staff for patients not requiring ventilator are at moderate risk and those dealing with SARI patients are at a high risk. The doctors working in field are also at a moderate risk of infection, while quarantined patients fall under low-risk group, except during clinical examination of symptomatic cases that pose moderate risk. All the high-risk groups should adhere to full PPE, moderate-risk group to N95 mask and gloves, while low-risk group requires three-layered mask with or without gloves.<sup>[150]</sup> The N95 masks are recommended for use by HCWs, patients and close contacts of the patients only. The WHO has

recommended the use of N95 masks only when performing aerosol-generating procedures or while having close contact with a suspect or confirmed case and not for the use by general public.<sup>[152]</sup> Owing to the shortage of N95 masks, sterilisation procedures such as ultraviolet irradiation, plasma sterilisation, treatment with hydrogen peroxide and moist heat and treatment with ethylene oxide have been successfully employed.<sup>[153-155]</sup> General public in areas with community spread should use the three-layered surgical mask or a cloth mask. Three-layered mask is not to be worn beyond 6 h or till it becomes wet as the respiratory droplets settled on the inner surface of the mask and may predispose more to bacterial contamination. The utmost care must be taken not to touch the potentially infectious outer surface of the mask. The lower strings followed by upper strings should be untied and the mask should be removed holding the upper strings.<sup>[150]</sup> One of the studies has compared the efficacy of cloth masks with medical masks in HCWs and found them to be less efficacious with ~97% penetration.<sup>[156]</sup> However, the CDC has recommended the use of cloth mask for general public in public settings with known community transmission, where social distancing is insurmountable. Cloth masks can be effortlessly washed with soap and water and re-used. These are not recommended for use in children <2 years of age, with breathing problems and incapacitated individuals having problems removing the mask on their own.<sup>[155]</sup> Effluent treatment plants should be set up in all the hospitals to render the hospital and laboratory waste non-infectious. E-learning modules ought to be prepared by apex institutions and circulated amongst staff, peripheral labs, private hospitals and laboratories to guide them efficiently on these aspects. The support from the administration is critical, and all attempts should be made to gear up the isolation facilities at primary and secondary level for management of patients with only mild symptoms so that only the critically ill patients requiring ventilator support are referred to tertiary care hospitals. Reverse triage system, which involves rapid handiwork of inundation capacity to handle the upsurge in cases by identifying those patients who do not require urgent medical assistance for 96 h and will not be harmed, if discharged early, can also be adopted if the pandemic worsens.<sup>[157]</sup>

Elective surgeries, including laparoscopic surgeries, need to be postponed until unless very urgent to minimise the risk to HCWs and patients, along with keeping the hospital uninhibited enough to deal with the rising number of cases.<sup>[158]</sup> Meanwhile, guidelines for apportioning dialysis patients have been proposed, advising the tele-health devices to be broadened so that visits for outpatients can be dwindled, on a transient basis.<sup>[159]</sup> The cardiac society has also advised to defer all the stenting and surgeries in ST-Elevation Myocardial Infarction (STEMI) patients, preferring the management with fibrinolytic agents, and a conservative approach for non-STEMI has been proposed.<sup>[160]</sup>

### Handling of dead bodies

Guidelines have been formulated for handling the dead body of COVID-19 patients to curtail the transmission. The

dead body should be placed in a leakproof plastic body bag, whose exterior ought to be decontaminated with 1% sodium hypochlorite. The bag is further wrapped with a mortuary sheet and is taken to the mortuary and later to the cremation ground. Only few relatives (four to six) should be allowed to perform the rituals. All the rituals that do not require touching the body can be performed and all the relatives and funeral or burial staff is sensitised that the body and ash does not pose any additional threat. Proper hand hygiene and decontamination of vehicle, isolation room and surfaces should be done using 1% sodium hypochlorite solution. All the waste generated in the diagnosis and treatment of patients is segregated in double-layered bags, and biomedical waste management guidelines should be strictly adhered to.<sup>[149,155]</sup>

### Home assessment of one and all

A novel approach of home assessment of all the individuals in a specific selected zone has been proposed based on the similar approach that was followed during the Ebola outbreak. This approach will be of surmount help to public health as well as the clinicians, reducing the cost and testing complexities. Special home assessment teams will be created for different regions, and the disease status of one and all will be assessed. This mode of approach exemplifies integrated and coordinated healthcare and is of immense help especially in outbreak and unconventional settings like cruises.<sup>[161]</sup>

### Vaccine

The best preventive strategy for the prevention of any infectious illness is the vaccine; the trials for the vaccine against SARS-CoV-2 are underway. Germany and the USA have claimed to make the vaccine available within few months. Currently, the National Institute of Health, Maryland, San Diego and Cambridge are working hard to develop the much-needed vaccine. Spike proteins are mainly being targeted for the same, to prevent the adhesion of virus to host cell, delimiting the invasion and spread. An mRNA-based approach is being used in Cambridge, however, San Diego claims to have developed DNA vaccine termed 'INO-4800', which will be available in market before this summer.<sup>[162]</sup> mRNA-1273 vaccine has shown satisfactory results in animal models and has entered open-label trial enrolling 45 adults, of age 18–55 years for 6 weeks, who will be administered vaccine at different dosages; 25, 100, 250 µg, to 15 persons each. The vaccine will be administered in two cycles, second one 28 days after the first dose. The vaccine will be administered intramuscularly in the upper arm.<sup>[163]</sup> Mycobacterium w is also one of the vaccine candidates under trials, in which 0.3 ml is being administered intradermally for three days, to critically-ill adult patients. Trials using S-glycoprotein subunit and cysteine chemokine receptor 5 (CCR5) antagonist are also in the pipeline.<sup>[162]</sup>

### Quarantine at home

The WHO has also issued advisory for the management of suspect mild cases at home, with special precautions to isolate the case in a dedicated, separate, well-ventilated room, with a single concierge, who should use mask all the time before

coming in contact with the affected person and should have a separate room, isolated from other persons at home, at a minimum distance of 1 m. Personal clothing, bed sheets, toilet seats and room should be cleaned stringently at regular intervals using soap and water or with 1 part bleach in 99 parts water, if desired. Clothes should be washed with detergent and water or by machine wash at 60°C–90°C. Disposable towels, gloves or aprons should be used.<sup>[164]</sup> Being an enveloped virus, it is easily destroyed by heat or detergents, thereby the terminal sterilisation is not that challenging. The ICMR has modelled the strategy of home quarantine and has speculated a decline by 62% in cases and a remarkable plummet of peak cases by 89%, effusively poleaxing the curve.<sup>[96]</sup>

### Surface cleaning

Surface cleaning should be done adequately with disinfectants such as sodium hypochlorite, as this is an enveloped virus, permissive to killing by alterations in cellular metabolism. Cleaning should be adequately done at home, hospitals, workplaces and airports to curtail the vicious cycle of transmission.<sup>[4]</sup> Cleaning of high-touch surfaces which include door handles, knobs, ventilators, trolleys, walls near toilet, rails of staircase, bedrails, drip stands, telephone, nursing counters and light switches, should be done using 1% of sodium hypochlorite with a contact period of 20 min and large blood spills with 10% hypochlorite solution with a contact period of 20 min. Surface cleaning, cots, wheels and patient care equipment ought to be thoroughly cleaned using Bacillol spray, floor with soap and water and toilet using Lysol® or phenol or as per country's specifications. The surfaces where bleach cannot be used should be treated with 70% isopropyl or ethyl alcohol. High-touch surfaces should be cleaned every 3–4 h, whereas low-touch surfaces such as walls and mirrors need to be cleaned only once daily.<sup>[155]</sup> Mobile phones should also be thoroughly disinfected periodically.

Breath analysers used by traffic police should also have disposable mouthpieces to prevent the transmission of microbes and viruses.

### Food safety and animal handling

Proper PPE, consisting of head cover, eye gear, tight-fitting mask, apron, impermeable gloves and shoe covers, should be worn while handling animal or animal products. PPE and the protective clothing should be discarded at workplace itself, as per the biomedical waste guidelines. and exposure of family members to soiled clothing or shoes should be avoided.<sup>[4,149]</sup>

Raw or undercooked meat should never be consumed. Proper heating of the food should be done to kill the organisms by thermal shock, as is a routine custom in India to properly heat the food before consumption.<sup>[4,149]</sup>

### Trade restrictions

The restriction on trade of Chinese items has not been imposed yet in view of the enveloped nature of virus, which makes it labile for easy destruction in the environment, but the same is still cryptic. If the virus turns out to be more stable and

transmitted via fomites, it can lead to havoc and huge economic losses, as many Chinese items have been traded till now, owing to the unknown mode of spread via fomites.<sup>[4,149]</sup>

### Public awareness

Currently, the mainstay of containing this outbreak is 'social distancing among all and quarantine of the suspected and confirmed cases separately', followed by an efficient and rapid diagnosis of the illness. Public awareness by means of visual display of posters demonstrating the spread, prevention and role of personal hygiene is being done on an upfront. 'Salaam Namaste campaigns' should be encouraged to lessen the contact and spread of such viruses. People of all strata, from school to offices and healthcare facilities, should be made aware of the significance of hand hygiene in curtailing the microbial transmission. Hand hygiene should be performed thoroughly following the six steps using an alcohol-based hand rub for 20 s or with soap and water for 40 s. Videos and posters should be displayed and circulated amongst the general public for the same.<sup>[165]</sup> Simultaneously, awareness regarding the onset, progress and prevention strategies can be circulated using social media as platform to approach maximum number of individuals in today's era. The general public is being channelled regarding the remunerations of lockdown to ensure minimum contact with each other so that transmission can be curtailed, and one and all can contribute altogether to contain the continuing infection. Webinars are also being conducted across the world to disseminate the updated information and best practices in management of the disease. Since the transmission of virus cannot be halted, the lockdown is to buy time for preparedness, delay the anthroponotic transmission and formulating stringent strategies for containment to prevent the spread till this pandemic becomes pan-endemic.<sup>[166]</sup>

The primary prerequisite to limit the transmission is an efficient triage system and segregation of cases along with stringent infection control measures. 'One health approach' is the mainstay for preventing emerging zoonosis by encompassing effective preventive strategies in all the following three arms: humans, animals and the environment. Another WHO initiative, Battle against Respiratory Viruses (BRaVe), is a multidisciplinary approach reinforcing research and innovation in the management of these viruses.<sup>[167]</sup> Open-access platforms such as International Severe Acute Respiratory and Emerging Infection Consortium, BioDiaspora and ProMed are available for partaking and stipulating comprehensive information for management. With the advent of extensive globalisation, travel and trade, it took merely few days for SARS-CoV-2 to jump from farm and forest to table and subsequently, to distant nations fetching a pandemic status. Emergence of this novel outbreak illustrates the urgent need to undertake comprehensive animal studies, with unambiguous reference to interspecies transmission, for understanding epidemiological, evolutionary and ecological drivers of such zoonosis.

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## Conflicts of interest

There are no conflicts of interest.

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