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Abdul Mannan
Deccan School of Pharmacy, Department of Pharmaceutics, Deccan School of Pharmacy, Dar-us-Salam, Aghapura, Hyderabad, Telangana, India

Ayesha Nausheen
Deccan School of Pharmacy, Department of Pharmaceutics, Deccan School of Pharmacy, Dar-us-Salam, Aghapura, Hyderabad, Telangana, India

Corresponding Author:
Ayesha Nausheen
Deccan School of Pharmacy, Department of Pharmaceutics, Deccan School of Pharmacy, Dar-us-Salam, Aghapura, Hyderabad, Telangana, India

A literature review of severe acute respiratory disorder (SARS): Corona virus

Abdul Mannan and Ayesha Nausheen

Abstract
Severe acute respiratory syndrome (SARS) is a newly emerged infectious viral disease in the 21st century that has posed an enormous threat to international health. In February and March 2003 there were major outbreaks of SARS in Hong Kong, Singapore, Vietnam, Taiwan, Canada, and other countries.
COVID-19 is not simialr to SARS as the virus that causes COVID-19 and the one that caused the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 are related to each other genetically, but the diseases they cause are quite different. SARS was more deadly but much less infectious than COVID-19. There have been no outbreaks of SARS anywhere in the world since 2003.
A novel coronavirus has been identified as the pathogen responsible for SARS. Several laboratories have completed sequencing the genome of the coronavirus that has led to the global epidemic of SARS, and noted that the SARS coronavirus (SARS CoV) is not closely related to any of the previously characterized corona viruses.
In this review article, we discuss the natural history, classification, evolution, transmission, diagnostics, epidemiological studies, clinical characterization and preventive measures of Severe Acute Respiratory Syndrome: Corona Virus.

Keywords: 2019-novel coronavirus, clinical characteristics, human transmission, Severe acute

Introduction

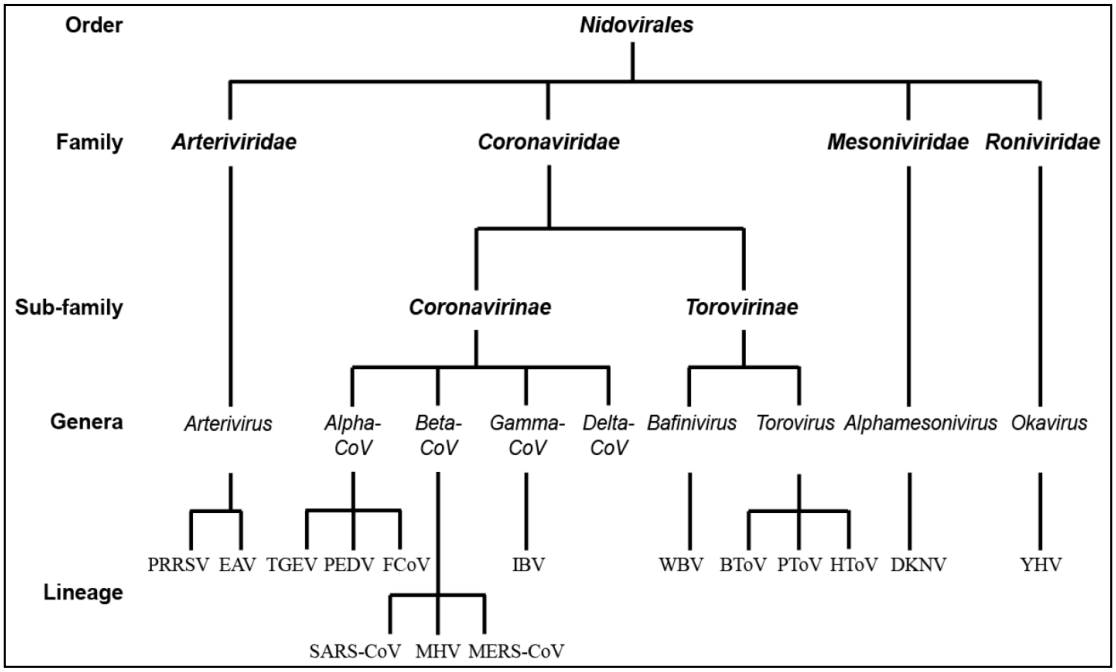
Natural History

Coronaviruses of humans were first identified more than 60 years ago from individuals with respiratory infections, mainly mild.
Coronaviruses of humans have been classified as a subfamily of the Coronaviridae family. The viruses are roughly spherical, enveloped particles 120–160 nm in diameter. Their name derives from the characteristic "crown"-like projections on their surface, approximately 20 nm long. They are positive-sense, single-stranded RNA viruses, are sensitive to heat and lipid solvents, and have a distinct replication strategy common to other viruses in the order Nidovirales. [1]
Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two highly transmissible and pathogenic viruses that emerged in humans at the beginning of the 21st century. Both viruses likely originated in bats, and genetically diverse corona viruses that are related to SARS-CoV and MERS-CoV were discovered in bats worldwide. The 2019-nCoV could be easily transmitted from human to human. At present, 67 the symptoms of secondary infection patients are relatively mild. [2]
The genome sequences suggest presence of a virus closely related to the members of a viral species termed severe acute respiratory syndrome (SARS)-related CoV, a species defined by the agent of the 2002/03 outbreak of SARS in humans. The species also comprises a large number of viruses mostly detected in rhinolophid bats in Asia and Europe. [3]
Epidemiological evidence suggested that most of those patients had been presented in a local seafood market in Wuhan and the virus gene sequence of patients was highly similar to that of bats and snakes. The viral 2019-nCoV was a kind of coronavirus that was very similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) which had caused more than 10000 cases and 1632 deaths across the globe [4].

Classification

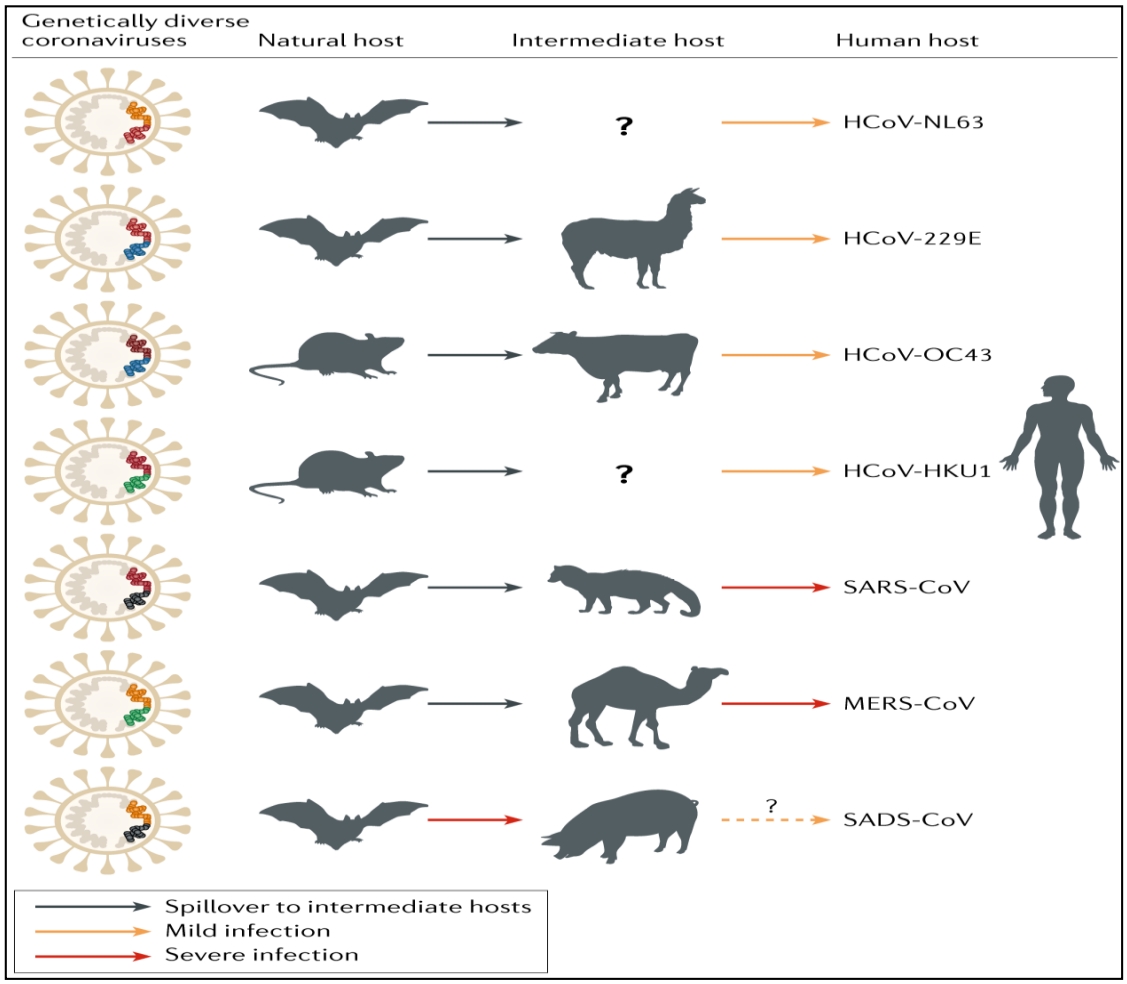
All human corona viruses (hCoVs) are enveloped, positive-strand RNA viruses and belong to the subfamily *Coronavirinae* in the family *Coronaviridae*, order *Nidovirales*. The subfamily *Coronavirinae* is further divided into three genera, *Alpha-*, *Beta-*, and *Gammacoronaviruses*, corresponding to the previous informal classification groups I, II, III,

respectively; there is also a recently recognized *Delta coronavirus* genus. [5]
Virus name: Human Corona Virus.
Order: *Nidovirales.*
Family: *Coronaviridae.*
Sub Family: *Coronavirinae.*
Genera: *Beta-CoV.*



At present, only members of alpha- and betacoronaviruses are known to infect humans. They differ from each other in nsp1 protein, which is distinct in size and sequence (gammacoronaviruses have no nsp1). Recently, MERS (Middle East respiratory syndrome) coronavirus, a novel human coronavirus in lineage C, has been isolated. [7]

Evolution



Coronaviruses cause respiratory and intestinal infections in animals and humans. They were not considered to be highly pathogenic to humans until the outbreak of severe acute respiratory syndrome (SARS) in 2002 and 2003 in Guangdong province, China as the corona viruses that circulated before that time in humans mostly caused mild infections in immunocompetent people. Ten years after SARS, another highly pathogenic coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Middle Eastern countries. SARS coronavirus (SARS-CoV) uses angiotensin-converting enzyme 2 (ACE2) as a receptor and primarily infects ciliated bronchial epithelial cells and type II pneumocytes, whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4; also known as CD26) as a receptor and infects unciliated bronchial epithelial cells and type II pneumocytes. SARS-CoV and MERS-CoV were transmitted directly to humans from market civets and dromedary camels, respectively, and both viruses are thought to have originated in bats. Extensive studies of these two important corona viruses have not only led to a better understanding of coronavirus biology but have also been driving coronavirus discovery in bats globally.

Transmission

Transmission was mostly limited to close contacts—those who had cared for, lived with, or had direct contact with the respiratory secretions or body fluids of a person with SARS. Large, virus-wladen respiratory droplets from symptomatic cases of SARS are deposited onto mucous membranes (eyes, nose, and mouth) or by contact with infectious agents. Saliva, tears, urine, and faeces also contain virus but have not been implicated in hospital-acquired infections when standard infection-control precautions are observed. Transmission from pregnant mothers to their babies has not been reported.

The route(s) of transmission have not been fully determined for some cases and clusters. Faecal aerosolization from faulty plumbing was implicated. Aerosolization spread is likely to have also been responsible for spread and in some hospitals, and may have been responsible for in-flight transmission. Environmental contamination with infectious respiratory secretions or other body fluids may have contributed to transmission. Although diarrhoea is common in SARS and viral shedding in faeces can be prolonged, true faecal-oral transmission did not appear to occur, and there are no reports of food or waterborne transmission. SARS-CoV was still infective for up to nine days in suspension and up to six days when dried.

Transmission Settings

1. **Hospital Transmission:** Hospitals were sites of transmission amplification, and the main site for SARS transmission. SARS cases were concentrated in hospitals and household contacts of SARS cases. In all outbreak sites, a large number of health-care workers were infected by the primary case presenting at their facility with atypical pneumonia of unknown aetiology. Later, the management or transfer of unrecognized cases led to continued transmission after control measures had been implemented.
2. Community-acquired infection has been associated with religious gatherings.
3. Overall, the risk of acquiring SARS from air travel, even before the second travel advisory, was extremely small.

Patient Characteristics

Most SARS transmissions were from sick people who had been hospitalized. As a result, 21% of all cases were health-care workers, with a range from 19% to 57% in the different outbreak sites. It also led to 53% of all cases being women, as they are over-represented among health-care workers.. All age groups were affected (age range 0-100 years, median age 42 years). It is not fully understood why SARS was uncommon in younger children, but it may be partly due to the fact that children were less likely to be exposed to SARS as a result of protective behaviors by exposed parents (especially healthcare workers) and a lower likelihood of exposure within health-care settings. Adolescents with SARS may develop severe disease requiring oxygen therapy or assisted ventilation. SARS acquired during pregnancy was associated with a high incidence of spontaneous miscarriage, preterm delivery, and intrauterine growth retardation. Pregnant women also experienced a higher case fatality rate. The case fatality rate in adults increased with age in all centers and exceeded 50% in cases aged 55 years and over. Overall, 20%–25% of cases required intensive care during their illness.

Asymptomatic infection and contribution to sars transmission

Serological surveys of populations at risk of SARS in 2003 found that asymptomatic infections were very uncommon. In Hong Kong, only two of 1,068 contacts of SARS cases (0.19%) who did not develop symptoms had SARS antibodies. A survey of 12,000 Hong Kong residents found only seven positive results (0.009%).59 In Taiwan, China, a survey of 623 healthy health-care workers who treated SARS patients found asymptomatic seroconversions in only two hospitals where four out of 433 health-care workers had SARS antibodies (0.92%).60 Most laboratory-confirmed SARS cases met the WHO clinical case definition (of severe disease), but mild infections have been reported.

Mild cases of infection with SARS-CoV may be difficult to detect, and could theoretically have been important in transmission. However, there is no evidence that they played an important role in transmission during the epidemic. Mild infections have not been implicated in super-spreading events. Despite close examination of contacts prior to symptoms, there was no observed transmission from asymptomatic infections. If asymptomatic transmission does occur, it must be extremely rare.

Modelling Control Measures: Isolation

The key epidemiological features of SARS, which were defined early on with limited information, remain valid. The most critical finding was that SARS transmission did not occur until after symptom onset, allowing early isolation of cases to terminate the outbreak. The main mode of transmission is through respiratory droplets that require close contact or transfer through fomites. However, under special circumstances, aerosolization can occur, leading to airborne spread. An outbreak of severe acute respiratory syndrome (SARS) was detected in Singapore at the beginning of March 2003. The outbreak, initiated by a traveler to Hong Kong, led to sequential spread of SARS to major acute–care hospitals in Singapore. [9]

Critical factors in containing this outbreak were

- Early detection and
- Complete assessment of movements and

- Follow-up of patients, healthcare workers, and visitors who were contacts.
- Visitor records were important in helping identify exposed persons who could carry the infection into the community.

In the three hospital outbreaks, three different containment strategies were used to contain spread of infection:

- closing an entire hospital,
- removing all potentially infected persons to a dedicated SARS hospital, and
- managing exposed persons in place.

On the basis of this experience, if a nosocomial (hospital) outbreak is detected late, a hospital may need to be closed in order to contain spread of the disease.

Outbreaks detected early can be managed by either removing all exposed persons to a designated location or isolating and managing them in place [10].

Diagnostics

Among the foremost priorities to facilitate public health interventions is reliable laboratory diagnosis. In acute respiratory infection, RT-PCR is routinely used to detect causative viruses from respiratory secretions. We have previously demonstrated the feasibility of introducing robust detection technology based on real-time RT-PCR in public health laboratories during international health emergencies by coordination between public and academic laboratories. In all of these situations, virus isolates were available as the primary substrate for establishing and controlling assays and assay performance. In the present case of 2019-nCoV, virus isolates or samples from infected patients have so far not become available to the international public health community. We report here on the establishment and validation of a diagnostic workflow for 2019-nCoV screening and specific confirmation, designed in absence of available virus isolates or original patient specimens. Design and validation were enabled by the close genetic relatedness to the 2003 SARS-CoV, and aided by the use of synthetic nucleic acid technology.

Methods

1. Clinical samples and coronavirus cell culture supernatants for initial assay evaluation
2. RNA extraction
3. Real-time reverse-transcription PCR
4. Specificity testing

1. Clinical samples and coronavirus cell culture supernatants for initial assay evaluation

Cell culture supernatants containing typed corona viruses and other respiratory viruses were provided by Charité and University of Hong Kong research laboratories. Respiratory samples were obtained during 2019 from patients hospitalized at Charité medical centre and tested by the NxTAG respiratory pathogen panel or in cases of MERS-CoV by the MERS-CoV upE assay as published before. Additional samples were selected from biobanks at Erasmus University Medical Center, Rotterdam, at Public Health England (PHE), London, and at the University of Hong Kong. Samples from all collections comprised sputum as well as nose and throat swabs with or without viral transport medium. Faecal samples containing bat-derived SARS-related CoV samples were tested. All synthetic RNA used in this study was photo metrically quantified.

2. RNA extraction

RNA was extracted from clinical samples with the MagNA Pure 96 system (Roche, Penzberg, Germany) and from cell culture supernatants with the viral RNA mini kit (QIAGEN, Hilden, Germany).

3. Real-time reverse-transcription PCR

A 25 µL reaction contained 5 µL of RNA, 12.5 µL of 2 × reaction buffer provided with the Superscript III one step RT-PCR system with Platinum Taq Polymerase (Invitrogen, Darmstadt, Germany; containing 0.4 mM of each deoxyribont triphosphates (dNTP) and 3.2 mM magnesium sulphate), 1 µL of reverse transcriptase/ Taq mixture from the kit, 0.4 µL of a 50 mM magnesium sulphate solution (Invitrogen), and 1 µg of nonacetylated bovine serum albumin (Roche). Primer and probe sequences, as well as optimised concentrations are shown in Table 1. All oligonucleotides were synthesised and provided by Tib-Molbiol (Berlin, Germany). Thermal cycling was performed at 55 °C for 10 min for reverse transcription, followed by 95 °C for 3 min and then 45 cycles of 95 °C for 15 s, 58 °C for 30 s. Participating laboratories used either Roche Light Cycler 480II or Applied Biosystems ViiA7 instruments (Applied Biosystems, Hong Kong, China).

TABLE 1

Primers and probes, real-time RT-PCR for 2019 novel coronavirus

Assay/use	Oligonucleotide	Sequence[a]	Concentration[b]
RdRP gene	RdRp_SARSr-F	GTGARATGGTCATGTGTGGCGG	Use 600 nM per reaction
	RdRp_SARSr-P2	FAM-CAGGTGGAACCTCATCAGGAGATGC-BBQ	Specific for 2019-nCoV, will not detect SARS-CoV. Use 100 nM per reaction and mix with P1
	RdRP_SARSr-P1	FAM-CCAGGTGGWACRTCATCMGGTGATGC-BBQ	Pan Sarbeco-Probe will detect 2019-nCoV, SARS-CoV and bat-SARS-related CoVs. Use 100 nM per reaction and mix with P2
	RdRp_SARSr-R	CARATGTTAAASACACTATTAGCATA	Use 800 nM per reaction
E gene	E_Sarbeco_F	ACAGGTACGTTAATAGTTAATAGCGT	Use 400 nm per reaction
	E_Sarbeco_P1	FAM-ACACTAGCCATCCTTACTGCGCTTCG-BBQ	Use 200 nm per reaction
	E_Sarbeco_R	ATATTGCAGCAGTACGCACACA	Use 400 nm per reaction
N gene	N_Sarbeco_F	CACATTGGCACCCGCAATC	Use 600 nm per reaction
	N_Sarbeco_P	FAM-ACTTCCTCAAGGAACAACATTGCCA-BBQ	Use 200 nm per reaction
	N_Sarbeco_R	GAGGAACGAGAAGAGGCTTG	Use 800 nm per reaction

[a] W is A/T; R is G/A; M is A/C; S is G/C. FAM: 6-carboxyfluorescein; BBQ: blackberry quencher.

[b] Optimised concentrations are given in nanomol per litre (nM) based on the final reaction mix, e.g. 1.5 µL of a 10 µM primer stock solution per 25 µL total reaction volume yields a final concentration of 600 nM as indicated in the table.

4. Protocol options and application notes

Laboratories participating in the evaluation used the TaqMan Fast Virus 1-Step Master Mix (Thermo Fisher) with the same oligonucleotide concentrations and cycling conditions. The QIAGEN One-Step RT-PCR Kit was also tested and found to be compatible. The intended cross-reactivity of all assays with viral RNA of SARS-CoV allows us to use the assays without having to rely on external sources of specific 2019-nCoV RNA. For a routine workflow, we recommend the E gene assay as the first-line screening tool, followed by confirmatory testing with the RdRp gene assay. Application of the RdRp gene assay with dual color technology can discriminate 2019-nCoV (both probes positive) from SARS-CoV RNA if the latter is used as positive control. Alternatively, laboratories may choose to run the RdRp assay with only the 2019-nCoV-specific probe.

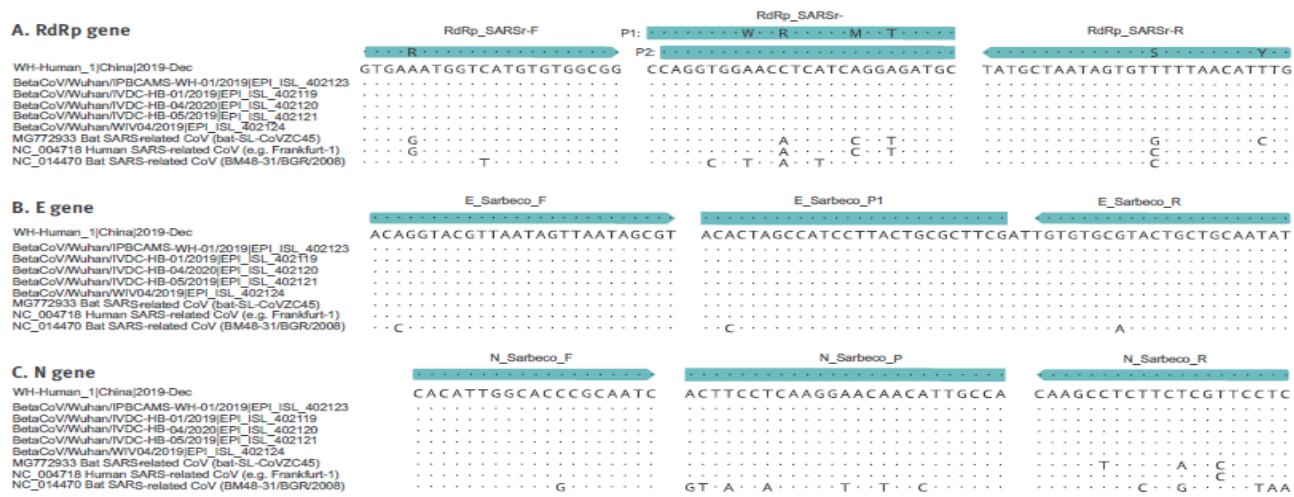
Ethical statement: The internal use of samples for diagnostic workflow optimization was agreed under the medical ethical rules of each of the participating partners.

Results

Before public release of virus sequences from cases of 2019-nCoV, the social media reports announcing detection of a SARS-like virus. It was assumed that a SARS-related CoV is involved in the outbreak. All complete and partial (if > 400 nt) SARS-related virus sequences available in GenBank by 1 January 2020 were downloaded. The list (n = 729 entries) was manually checked and artificial sequences (laboratory-derived, synthetic, etc), as well as sequence duplicates were removed, resulting in a final list of 375 sequences. These sequences were aligned and the alignment was used for assay design (Supplementary Figure S1). Upon release of the first 2019-nCoV sequence, three assays were selected based on how well they matched to the 2019-nCoV genome (Figure 1). The alignment was complemented by additional sequences released independently on GISAID confirming the good matching of selected primers to all sequences. Alignments of primer binding domains with 2019-nCoV, SARS-CoV as well as selected bat-associated SARS-related CoV are shown in Figure 2.

FIGURE 2

Partial alignments of oligonucleotide binding regions, SARS-related coronaviruses (n = 9)



The panels show six available sequences of 2019-nCoV, aligned to the corresponding partial sequences of SARS-CoV strain Frankfurt 1, which can be used as a positive control for all three RT-PCR assays. The alignment also contains a closely related bat virus (Bat SARS-related CoV isolate bat-SL-CoVZC45, GenBank accession number MG772933) as well as the most distant member within the SARS-related bat CoV clade, detected in Bulgaria (GenBank accession number NC_014470). Dots represent identical nucleotides compared with the WH_Human_1 sequence. Nucleotide substitutions are specified. Blue arrows: oligonucleotides as specified in Table 1. More comprehensive alignments can be found in the Supplement.

Detection range for SARS-related corona viruses from bats

At present, the potential exposure to a common environmental source in early reported cases implicates the possibility of independent zoonotic infections with increased sequence variability To show that the assays can detect other bat-associated SARS-related viruses, we used the E gene assay to test six bat derived faecal samples These virus-positive samples stemmed from European rhinolophid bats. Detection of these phylogenetic outliers within the SARS-related CoV clade suggests that all Asian viruses are likely to be detected. This would, theoretically, ensure broad sensitivity even in case of multiple independent acquisitions of variant viruses from an animal reservoir.

Conclusion from above techniques

The present report describes the establishment of a diagnostic workflow for detection of an emerging virus in the absence of physical sources of viral genomic nucleic acid. Effective assay design was enabled by the willingness of scientists from China to share genome information before formal publication, as well as the availability of broad sequence knowledge from ca 15 years of investigation of SARS-related viruses in animal reservoirs. The relative ease with which assays could be designed for this virus, in contrast to SARS-CoV in 2003, proves the huge collective value of descriptive studies of disease ecology and viral genome diversity. Real-time RT-PCR is widely deployed in diagnostic virology. In the case of a public health emergency, proficient diagnostic laboratories can rely on this robust technology to establish new diagnostic tests within their routine services before pre-formulated assays become available. In addition to information on reagents, oligonucleotides and positive controls, laboratories working under quality control programmes need to rely on documentation of technical qualification of the assay formulation as well as data from external clinical evaluation

tests. The provision of control RNA templates has been effectively implemented by the EVAg project that provides virus-related reagents from academic research collections. SARS CoV RNA was retrievable from EVAg before the present outbreak; specific products such as RNA transcripts for the here-described assays were first retrievable from the EVAg online catalogue on 14 January 2020. Technical qualification data based on cell culture materials and synthetic constructs, as well as results from exclusivity testing on 75 clinical samples, were included in the first version of the diagnostic protocol provided to the WHO on 13 January 2020. Based on efficient collaboration in an informal network of laboratories, these data were augmented within 1 week comprise testing results based on a wide range of respiratory pathogens in clinical samples from natural infections. Comparable evaluation studies during regulatory qualification of in vitro diagnostic assays can take months for organization, legal implementation and logistics and typically come after the peak of an outbreak has waned. The speed and effectiveness of the present deployment and evaluation effort were enabled by national and European research networks established in response to international health crises in recent years, demonstrating the enormous response capacity that can be released through coordinated action of academic and public laboratories. This laboratory capacity not only supports immediate public health interventions but enables sites to enrol patients during rapid clinical research responses [11].

Selected diagnostic tests for SARS-Cov-2 [12]

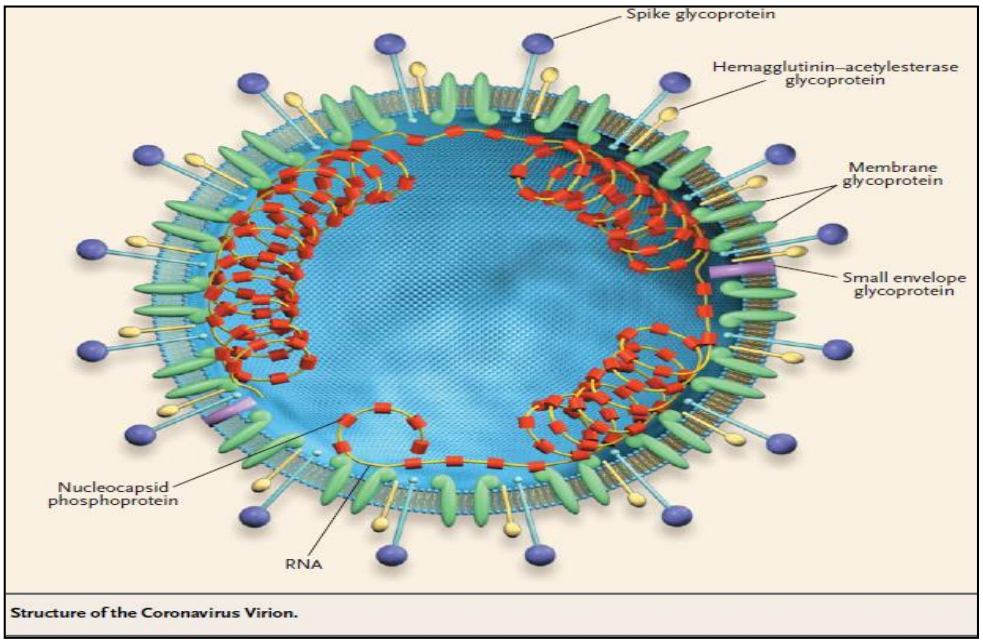
S. No	Developer	Test	Description	Current status
	Chinese National Institute for Viral Disease Control and Prevention	New coronavirus nucleic acid assay	Primers and probes for detecting the Novel coronavirus with RT-PCR	In widespread distribution in China
	US Centers for Disease Control and Prevention (CDC)	CDC 2019-nCoV real-time reverse Transcriptase PCR	PCR test that runs on Applied Biosystems7500 Fast Dx RT PCR instrument with SDS 1.4 software	Emergency Use Authorization (EUA) granted by the FDA on 4 February
	University of Hong Kong	Real-time reverse Transcriptase PCR assays	Two single-step quantitative RT reverse Transcription PCR assays for *N* gene and *ORF1b* of sarbecovirus subgenus	Reference test shipped to WHO and to over 30 labs globally
	Amoy Diagnostics (Xiamen, China)	Coronavirus gene detection kit	PCR-based rapid detection kit	Seeking emergency approval from China's National Medical Products Administration
	Altona Diagnostics (Hamburg, Germany)	Real-time PCR assay	Rapid detection of coronavirus RNA from Respiratory samples	In development; Shipping expected end of February
	BGI Group (Beijing)	Real-time Fluorescent RTPCR kit for detecting 2019 nCoV	Test results delivered in several hours	Emergency approval granted by China's National Medical Products Administration
	Novacyt, Primerdesign	Novel Coronavirus Strain 2019 nCoV	Runs on portable genesig16 RT PCR instrument; delivers test results in less than two hours	CE-marked research use only test launched 17 February; seeking FDA EUA
	Thermo Fisher Scientific	TaqMan 2019 nCoV Assay Kit	Lab PCR test that runs on Applied Biosystems 7500 RT-PCR system; identifies sequences found in initial SARS-CoV-2 genomes	Research use only
	Qiagen (Hilden, Germany)	QIAstat-Dx Respiratory 2019-nCoV Panel	Integrated sample prep and RT-PCR detection of 21 respiratory pathogens; samples and reagents delivered in assay cartridges and analyzed in desktop QIAstat-Dx Analyzer; results delivered in one hour	Prototype panel Including COVID-19 test shipped on 11 February for clinical performance assessment in China and Europe
	Biomeme	Biomeme COVID-19 Go Strips	Integrated sample prep and RNA detection test that runs on Biomeme's mobile handheld quantitative PCR device	Research use only
	Agency for Science, Technology and Research (A*STAR), MiRXES (both Singapore)	Fortitude Kit 2.0	RT-PCR SARS CoV-2 assay	100,000 tests produced; provisional authorization received from Health Sciences Authority, Singapore
	TIB Molbiol (Berlin, Germany) also via Roche Diagnostics	SARS-CoV-2 E, RdRP or N gene CE-IVD 7 virus Respiratory Panel multiplex RT PCR	1-step RT PCR	Launched January. 20,000 kits shipped to over 70 countries

Epidemiological Studies

The discovery that a novel coronavirus is the probable cause of the newly recognized severe acute respiratory syndrome (SARS), provides a dramatic example of an emerging coronavirus disease in humans. Although human corona viruses cause up to 30 percent of colds, they rarely cause lower respiratory tract disease. In contrast, corona viruses cause devastating epizootics of respiratory or enteric disease in livestock and poultry [13].

Structure: Most corona viruses cause disease in only one host species. All known corona viruses are found in three serologically unrelated groups. The Figure shows the structure of the virion. The messagesense RNA genome and the viral nucleocapsid phosphoprotein form a helical nucleocapsid. A corona of large, distinctive spikes in the envelope makes

possible the identification of corona viruses by electron microscopy. The spikes, oligomers of the spike(S) glycoprotein, bind to receptors on host cells and fuse the viral envelope with host cell membranes.



Structure of the Coronavirus Virion.

Coronaviruses in group 2 also have a hemagglutinin–acetylesterase (HE) glycoprotein that binds to sugar moieties on cell membranes. Curiously, the gene for HE was apparently introduced into an ancestral coronavirus genome by recombination with the messenger RNA encoding HE of influenza C. The unique RNA-dependent RNA polymerase of corona viruses often switches template strands during replication, causing RNA recombination when a cell is infected with several corona viruses. This error-prone polymerase also generates point mutations and large deletions or insertions of foreign RNA into the viral genome. The SARS-associated coronavirus could have arisen as a mutant of a human coronavirus that acquired new virulence factors, as a mutant of an animal coronavirus that can infect human cells, or as a recombinant of two human corona viruses or a human coronavirus and an animal coronavirus [14].

Antibodies to the SARS-associated coronavirus: Antibodies to the SARS-associated coronavirus were found in serum samples obtained from patients with SARS during convalescence but not in human serum samples banked before the SARS outbreak, suggesting that the SARS-associated coronavirus is new to the human population. The nucleotide sequence of the SARS-associated coronavirus genome differs substantially from sequences of all known corona viruses. Thus, the SARS-associated coronavirus is neither a mutant of any known coronavirus nor a recombinant of known corona viruses. It is a previously unknown coronavirus, probably from a nonhuman host, that somehow acquired the ability to infect humans. Serologic tests of wild and domestic animals and birds in the region where the outbreak first appeared may identify the usual host. The host range, tissue tropism, and virulence of animal corona viruses can be changed by mutations in the S gene. The sequence of the S gene in the SARS-associated coronavirus may suggest how S glycoprotein affects the pathogenesis of SARS. It is an amazing feat that the SARS-associated coronavirus genome has been completely sequenced so quickly. The surprising discovery that the virus can be readily isolated in a monkey-kidney cell line was the key to the rapid molecular characterization of this novel coronavirus and the development of diagnostic tests for SARS. SARS-associated coronavirus has recently been proved to be the cause of SARS. Both viral and host factors affect the virulence of coronavirus diseases in animals. The disease is usually most severe in neonates. The signs of infection in immunosuppressed animals may differ from those in immunocompetent animals; immunosuppressed animals may also shed virus for prolonged periods and accumulate and possibly spread mutant viruses. The detection of SARS-associated coronavirus in fecal and serum samples from patients, as well as in respiratory specimens, suggests that this virus, like many animal corona viruses, may be spread both by fecal contamination and by respiratory droplets. Co infection with other viruses, parasites, or bacteria exacerbates some animal coronavirus diseases. The deaths of 3 to 4 percent of patients with SARS may result from host factors that exacerbate the disease. Although there are no approved drugs with proven efficacy against corona viruses, there are potential targets for the development of new drugs. Protease inhibitors could prevent processing of the RNA polymerase or cleavage of the viral S glycoprotein. Inhibitors of coronavirus acetyl esterase activity might limit viral replication, as neuraminidase inhibitors inhibit the replication of influenza viruses A and B. Inhibitors of membrane fusion might block viral entry, as do several new drugs against the human immunodeficiency virus. Antibodies against the viral S glycoprotein or the unidentified receptor for the SARS-associated coronavirus might also block entry of the virus. Vaccines are available for some animal corona viruses. Vaccination with live, attenuated virus is effective against porcine epidemic diarrhea virus and avian infectious bronchitis virus. However, recombination of genomes of vaccine strains with wild type corona viruses is a potential risk associated with using live, attenuated coronavirus vaccines in humans. Killed or subunit vaccines containing the spike glycoprotein, perhaps with other viral proteins, might prevent lower respiratory tract disease in humans. However, some vaccines against feline corona viruses actually enhanced disease when vaccinated animals were exposed to wild-type

virus, and antibody enhancement of disease is a potential risk of SARS vaccines in humans. It is possible that the current outbreak may be controlled and the virus eliminated by quarantine alone. Nevertheless, it is prudent to develop safe, effective drugs and vaccines.

Clinical Characterisation and Management

In the early stages of this pneumonia, severe acute respiratory infection symptoms occurred, with some patients rapidly developing acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications. On Jan 7, a novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and was subsequently named 2019-nCoV by WHO. Coronaviruses can cause multiple system infections in various animals and mainly respiratory tract infections in humans, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Most patients have mild symptoms and good prognosis. So far, a few patients with 2019-nCoV have developed severe pneumonia, pulmonary edema, ARDS, or multiple organ failure and have died. All costs of 2019-nCoV treatment are covered by medical insurance in China. At present, information regarding the epidemiology and clinical features of pneumonia caused by 2019-nCoV is scarce [15].

On admission after pneumonia like symptoms, most patients had fever or cough and a third of patients had shortness of breath. Other symptoms included muscle ache, headache, confusion, chest pain, and diarrhea. Many patients presented with organ function damage, including 17 (17%) with ARDS, eight (8%) with acute respiratory injury, three (3%) with acute renal injury, four (4%) with septic shock, and one (1%) with ventilator-associated pneumonia. On admission, leucocytes were below the normal range in nine (9%) patients and above the normal range in 24 (24%) patients. 38 (38%) patients had neutrophils above the normal range. Lymphocytes and hemoglobin were below the normal range in many patients. Platelets were below the normal range in 12 (12%) patients and above the normal range in four (4%). 43 patients had differing degrees of liver function abnormality, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the normal range; one patient had severe liver function damage. Most patients had abnormal myocardial zymogram, which showed the elevation of creatine kinase in 13 (13%) patients and the elevation of lactate dehydrogenase in 75 (76%) patients, one of whom also showed abnormal creatine kinase (6280 U/L) and lactate dehydrogenase. Seven (7%) patients had different degrees of renal function damage, with elevated blood urea nitrogen or serum creatinine. Regarding the infection index, procalcitonin was above the normal range in six (6%) patients. Most patients had serum ferritin above the normal range. 73 patients were tested for C -reactive protein, most of whom had levels above the normal range. All patients were tested for nine respiratory pathogens and the nucleic acid of influenza viruses A and B. Bacteria and fungi culture were done at the same time. We did not find other respiratory viruses in any of the patients. Acinetobacter baumannii, Klebsiella pneumoniae, and Aspergillus flavus were all cultured in one patient. A baumannii turned out to be highly resistant to antibiotics. One case of fungal infection was diagnosed as Candida glabrata and three cases of fungal infection were diagnosed as Candida albicans. According to chest x -ray and CT, 74 (75%) patients showed bilateral pneumonia (75%) with just 25 (25%) patients showing unilateral pneumonia. 14 (14%) patients showed multiple mottling and ground glass opacity. Additionally, pneumothorax occurred in one (1%) patient [16].

All patients were treated in isolation. 75 (76%) patients received antiviral treatment, including oseltamivir (75 mg every 12 h, orally), ganciclovir (0·25 g every 12 h, intravenously), and lopinavir and ritonavir tablets (500 mg twice daily, orally). The duration of antiviral treatment was 3–14 days. Most patients were given antibiotic treatment; 25 (25%) patients were treated with a single antibiotic and 45 (45%) patients were given combination therapy. The antibiotics used generally covered common pathogens and some atypical pathogens; when secondary bacterial infection occurred, medication was administered according to the results of bacterial culture and drug sensitivity. The antibiotics used were cephalosporins, quinolones, carbapenems, tigecycline against methicillin-resistant Staphylococcus aureus, linezolid, and antifungal drugs. The duration of antibiotic treatment was 3-17 days. 19 (19%) patients were also treated with methylprednisolone sodium succinate, methylprednisolone, and dexamethasone for 3–15 days. 13 patients used non-invasive ventilator mechanical ventilation for 4-22 days. Four patients used an invasive ventilator to assist ventilation for 3-20 days. The ventilator adopted P-SIMV mode, the inhaled oxygen concentration was 35-100%, and the positive end expiratory pressure was 6-12 cm H2O. All four patients were still using ventilators at data cutoff. Moreover, nine (9%) patients received continuous blood purification due to renal failure and three (3%) patients were treated with extracorporeal membrane oxygenation (ECMO; table 2). By the end of Jan 25, 31 (31%) patients had been discharged and 11 (11%) patients had died; all other patients were still in hospital. The first two deaths were a 61-year-old man (patient 1) and a 69-year-old man (patient 2). They had no previous chronic underlying disease but had a long history of smoking. Patient 1 was transferred to Jinyintan Hospital and diagnosed with severe pneumonia and ARDS. He was immediately admitted to the intensive care unit (ICU) and given an incubated ventilator-assisted breathing therapy. Later, the patient, having developed severe respiratory failure, heart failure, and sepsis, experienced a sudden cardiac arrest on the 11th day of admission and was declared dead. Patient 2 had severe pneumonia and ARDS after admission. The patient was transferred to the ICU and given ventilator-assisted breathing, and received antiinfection and ECMO treatment after admission. The patient's hypoxemia remained unresolved. On the ninth day of admission, the patient died of severe pneumonia, septic shock, and respiratory failure. The intervals between the onset of symptoms and the use of ventilator assisted breathing in the two patients were 3 days and 10 days, respectively. The course of the disease and lung lesions progressed rapidly in both patients, with both developing multiple organ failure in a short time. The deaths of these two patients were consistent with the MuLBSTA score, an early warning model for predicting mortality in viral pneumonia. 8 of the remaining nine patients who died, eight patients had lymphopenia, seven had bilateral pneumonia, five were older than 60 years, three had hypertension, and one was a heavy smoker [17].

	Patients (n=99)
Age, years	
Mean (SD)	55·5 (13·1)
Range	21–82
≤39	10 (10%)
40–49	22 (22%)
50–59	30 (30%)
60–69	22 (22%)
≥70	15 (15%)
Sex	
Female	32 (32%)
Male	67 (68%)
Occupation	
Agricultural worker	2 (2%)
Self-employed	63 (64%)
Employee	15 (15%)
Retired	19 (19%)
Exposure to Huanan seafood market*	49 (49%)
Long-term exposure history	47 (47%)
Short-term exposure history	2 (2%)
Chronic medical illness	50 (51%)
Cardiovascular and cerebrovascular diseases	40 (40%)
Digestive system disease	11 (11%)
Endocrine system disease†	13 (13%)
Malignant tumour	1 (1%)
Nervous system disease	1 (1%)
Respiratory system disease	1 (1%)
Admission to intensive care unit	23 (23%)
Clinical outcome	
Remained in hospital	57 (58%)
Discharged	31 (31%)
Died	11 (11%)

Data are n (%) unless specified otherwise. 2019-nCoV=2019 novel coronavirus. *Long-term exposure is having worked at or lived in or around Huanan seafood market, whereas short-term exposure is having been to Huanan seafood market occasionally. †12 were diabetic.

Table 1: Demographics, baseline characteristics, and clinical outcomes of 99 patients admitted to Wuhan Jinyintan Hospital (Jan 1–20, 2020) with 2019-nCoV pneumonia

	Patients (n=99)
Signs and symptoms at admission	
Fever	82 (83%)
Cough	81 (82%)
Shortness of breath	31 (31%)
Muscle ache	11 (11%)
Confusion	9 (9%)
Headache	8 (8%)
Sore throat	5 (5%)
Rhinorrhoea	4 (4%)
Chest pain	2 (2%)
Diarrhoea	2 (2%)
Nausea and vomiting	1 (1%)
More than one sign or symptom	89 (90%)
Fever, cough, and shortness of breath	15 (15%)
Comorbid conditions	
Any	33 (33%)
ARDS	17 (17%)
Acute renal injury	3 (3%)
Acute respiratory injury	8 (8%)
Septic shock	4 (4%)
Ventilator-associated pneumonia	1 (1%)
Chest x-ray and CT findings	
Unilateral pneumonia	25 (25%)
Bilateral pneumonia	74 (75%)
Multiple mottling and ground-glass opacity	14 (14%)
Treatment	
Oxygen therapy	75 (76%)
Mechanical ventilation	
Non-invasive (ie, face mask)	13 (13%)
Invasive	4 (4%)
CRRT	9 (9%)
ECMO	3 (3%)
Antibiotic treatment	70 (71%)
Antifungal treatment	15 (15%)
Antiviral treatment	75 (76%)
Glucocorticoids	19 (19%)
Intravenous immunoglobulin therapy	27 (27%)

2019-nCoV=2019 novel coronavirus. ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. CRRT=continuous renal replacement therapy.

Table 2: Clinical characteristics and treatment of patients with 2019-nCoV pneumonia

	Patients (n=99)
Blood routine	
Leucocytes (x 10⁹ per L; normal range 3·5–9·5)	7·5 (3·6)
Increased	24 (24%)
Decreased	9 (9%)
Neutrophils (x 10⁹ per L; normal range 1·8–6·3)	5·0 (3·3–8·1)
Increased	38 (38%)
Lymphocytes (x 10⁹ per L; normal range 1·1–3·2)	0·9 (0·5)
Decreased	35 (35%)
Platelets (x 10⁹ per L; normal range 125·0–350·0)	213·5 (79·1)
Increased	4 (4%)
Decreased	12 (12%)
Haemoglobin (g/L; normal range 130·0–175·0)	129·8 (14·8)
Decreased	50 (51%)
Coagulation function	
Activated partial thromboplastin time (s; normal range 21·0–37·0)	27·3 (10·2)
Increased	6 (6%)
Decreased	16 (16%)
Prothrombin time (s; normal range 10·5–13·5)	11·3 (1·9)
Increased	5 (5%)
Decreased	30 (30%)
D-dimer (μg/L; normal range 0·0–1·5)	0·9 (0·5–2·8)
Increased	36 (36%)
Blood biochemistry	
Albumin (g/L; normal range 40·0–55·0)	31·6 (4·0)
Decreased	97 (98%)
Alanine aminotransferase (U/L; normal range 9·0–50·0)	39·0 (22·0–53·0)
Increased	28 (28%)
Aspartate aminotransferase (U/L; normal range 15·0–40·0)	34·0 (26·0–48·0)
Increased	35 (35%)
Total bilirubin (μmol/L; normal range 0·0–21·0)	15·1 (7·3)
Increased	18 (18%)
Blood urea nitrogen (mmol/L; normal range 3·6–9·5)	5·9 (2·6)
Increased	6 (6%)
Decreased	17 (17%)
Serum creatinine (μmol/L; normal range 57·0–111·0)	75·6 (25·0)
Increased	3 (3%)
Decreased	21 (21%)
Creatine kinase (U/L; normal range 50·0–310·0)	85·0 (51·0–184·0)
Increased	13 (13%)
Decreased	23 (23%)
Lactate dehydrogenase (U/L; normal range 120·0–250·0)	336·0 (260·0–447·0)
Increased	75 (76%)
Myoglobin (ng/mL; normal range 0·0–146·9)	49·5 (32·2–99·8)
Increased	15 (15%)
Glucose (mmol/L; normal range 3·9–6·1)	7·4 (3·4)
Increased	51 (52%)
Decreased	1 (1%)
(Table 3 continues in next column)	

(Continued from previous column)

	Patients (n=99)
Infection-related biomarkers	
Procalcitonin (ng/mL; normal range 0·0–5·0)	0·5 (1·1)
Increased	6 (6%)
Interleukin-6 (pg/mL; normal range 0·0–7·0)	7·9 (6·1–10·6)
Increased	51 (52%)
Erythrocyte sedimentation rate (mm/h; normal range 0·0–15·0)	49·9 (23·4)
Increased	84 (85%)
Serum ferritin (ng/mL; normal range 21·0–274·7)	808·7 (490·7)
Increased	62 (63%)
C-reactive protein (mg/L; normal range 0·0–5·0)*	51·4 (41·8)
Increased	63/73 (86%)
Co-infection	
Other viruses	0
Bacteria	1 (1%)
Fungus	4 (4%)

Data are n (%), n/N (%), mean (SD), and median (IQR). Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range. 2019-nCoV=2019 novel coronavirus. *Data available for 73 patients.

Table 3: **Laboratory results of patients with 2019-nCoV pneumonia**

Preventive Measures

Preventive measures to reduce the chances of infection in locations with an outbreak of the disease are similar to those published for other corona viruses:

According to the WHO,

- Stay home,
- Avoid travel and public activities,
- Wash hands with soap and hot water often,
- Practice good respiratory hygiene,
- Avoid touching the eyes, nose, or mouth with unwashed hands,
- The use of masks is only recommended if a person is coughing or sneezing or when one is taking care of someone with a suspected infection,
- Social distancing strategies aim to reduce contact of infected persons with large groups by closing schools and workplaces, restricting travel and canceling mass gatherings [18]

To prevent transmission of the virus, the US Centers for Disease Control and Prevention (CDC) recommends that

- The infected individuals stay home except to get medical care, call ahead before visiting a healthcare provider,
- Wear a face mask when exposed to an individual or location of a suspected infection,
- Cover coughs and sneezes with a tissue,
- Regularly wash hands with soap and water and
- Avoid sharing personal household items.
- The CDC also recommends that individuals wash hands often with soap and water for at least 20 seconds, especially after going to the toilet or when hands are visibly dirty, before eating and after blowing one's nose, coughing, or sneezing [19]
- It further recommended using an alcohol-based hand

sanitizer with at least 60% alcohol, but only when soap and water are not readily available.

- The WHO advises individuals to avoid touching the eyes, nose, or mouth with unwashed hands.
- Spitting in public places also should be avoided [20].

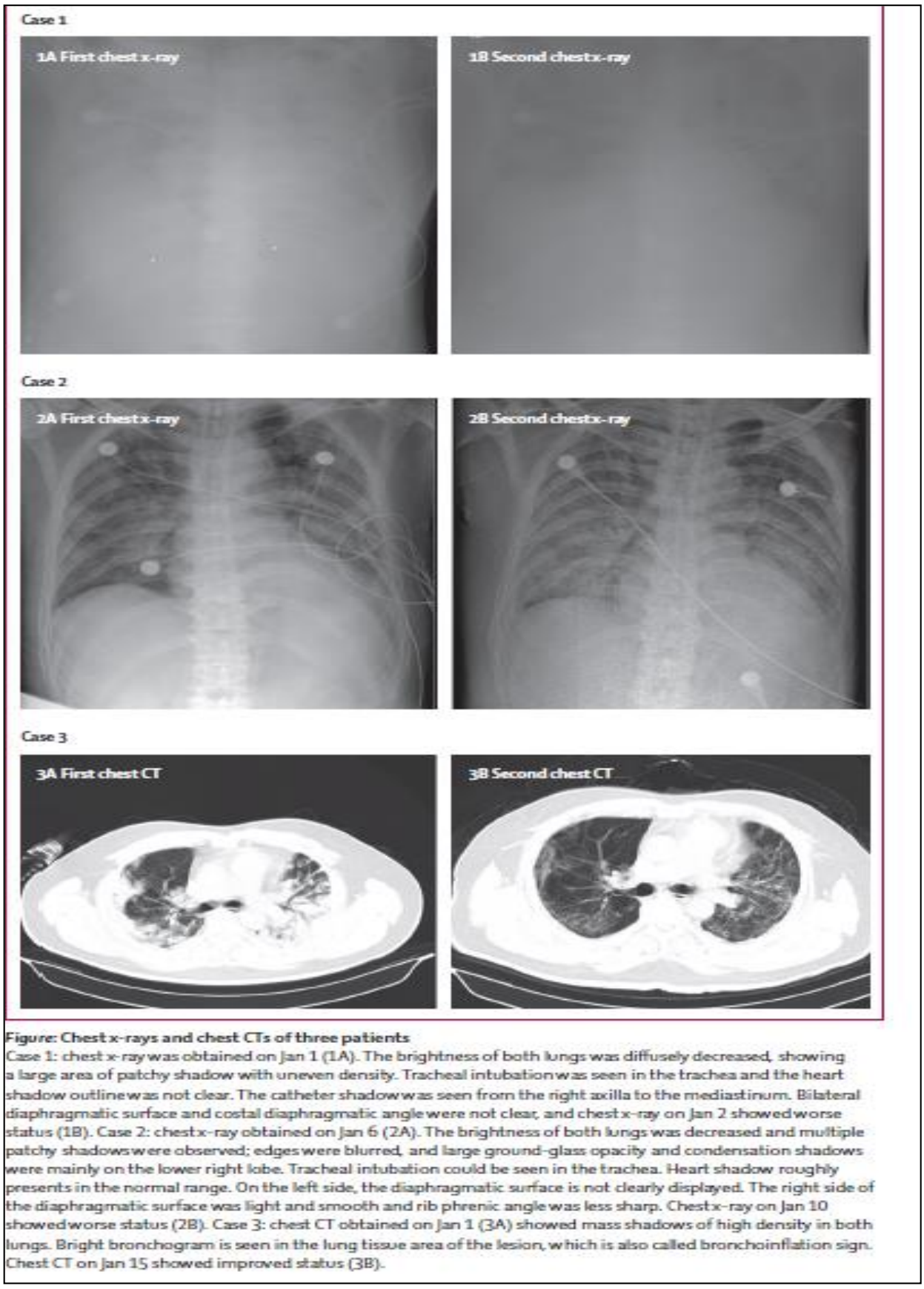


Figure: Chest x-rays and chest CTs of three patients
Case 1: chest x-ray was obtained on Jan 1 (1A). The brightness of both lungs was diffusely decreased, showing a large area of patchy shadow with uneven density. Tracheal intubation was seen in the trachea and the heart shadow outline was not clear. The catheter shadow was seen from the right axilla to the mediastinum. Bilateral diaphragmatic surface and costal diaphragmatic angle were not clear, and chest x-ray on Jan 2 showed worse status (1B). Case 2: chest x-ray obtained on Jan 6 (2A). The brightness of both lungs was decreased and multiple patchy shadows were observed; edges were blurred, and large ground-glass opacity and condensation shadows were mainly on the lower right lobe. Tracheal intubation could be seen in the trachea. Heart shadow roughly presents in the normal range. On the left side, the diaphragmatic surface is not clearly displayed. The right side of the diaphragmatic surface was light and smooth and rib phrenic angle was less sharp. Chest x-ray on Jan 10 showed worse status (2B). Case 3: chest CT obtained on Jan 1 (3A) showed mass shadows of high density in both lungs. Bright bronchogram is seen in the lung tissue area of the lesion, which is also called bronchoinflation sign. Chest CT on Jan 15 showed improved status (3B).

Conclusion

Corona viruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronavirus disease (COVID-19) is a new strain that was

discovered in 2019 and has not been previously identified in humans.

Corona viruses are zoonotic, meaning they are transmitted between animals and people. Detailed investigations found that SARS-CoV was transmitted from civet cats to humans and MERS-CoV from dromedary camels to humans. Several known corona viruses are circulating in animals that have not yet infected humans.

Common signs of infection include respiratory symptoms, fever, and cough, shortness of breath and breathing difficulties. In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death. The most common symptoms of COVID-19 are fever, tiredness, and dry cough. Some patients may have aches and pains, nasal congestion, runny nose, sore throat or diarrhea. These symptoms are usually mild and begin gradually. Some people become infected but don't develop any symptoms and don't feel unwell. Most people (about 80%) recover from the disease without needing special treatment. Around 1 out of every 6 people who gets COVID-19 becomes seriously ill and develops difficulty breathing. Older people, and those with underlying medical problems like high blood pressure, heart problems or diabetes, are more likely to develop serious illness.

Standard recommendations to prevent infection spread include regular hand washing, covering mouth and nose when coughing and sneezing, thoroughly cooking meat and eggs. Avoid close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing. People with fever, cough and difficulty breathing should seek medical attention.

Older persons and persons with pre-existing medical conditions (such as high blood pressure, heart disease, lung disease, cancer or diabetes) appear to develop serious illness more often than others.

COVID-19 is not similar to SARS as the virus that causes COVID-19 and the one that caused the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 are related to each other genetically, but the diseases they cause are quite different.

SARS was more deadly but much less infectious than COVID-19. There have been no outbreaks of SARS anywhere in the world since 2003.

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