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KEY WORDS

Coronavirus, Covid-19, Pandemia, special edition, transmission, literature review, Wuhan, China, Italy, Spain, USA, SARS-CoV-2.

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REVIEW ARTICLE

Coronavirus and COVID-19: The latest news and views from the scientific community about the new coronavirus and COVID-19.

Introduction: Coronavirus is a family of viruses that cause respiratory infections. The new coronavirus agent was discovered on 12/31/19 after cases registered in China. It causes the disease called coronavirus (COVID-19). The first human coronaviruses were isolated for the first time in 1937. However, it was in 1965 that the virus was described as coronavirus, due to the profile under microscopy, looking like a crown.

Objectives: This article aims to bring the most current medical literature on the coronavirus pandemic (COVID-19).

Methodology: The publications with the greatest impact factor in February and March 2020 were searched in Nature, Elsevier, JAMA and Wiley.

Results: More than 200 articles on COVID-19 were found and 20 articles were selected with the highest number of citations on Google Scholar.

Conclusion: Until March 2020, there is no really effective treatment against COVID-19, but many medications are being tested and with very promising results. The concern with the economy is also an extremely relevant factor at this moment.

INTRODUCTION

To support urgent research to combat the ongoing outbreak of COVID-19, caused by the new coronavirus SARS-CoV-2, the BJHS Research editorial team selected from the medical literature of 2020 a collection of relevant articles. This collection includes research on the basic biology of coronavirus infection, its detection, treatment and evolution, research on the epidemiology of emerging viral diseases and opinions of the most relevant researchers in the area published in the high impact journals.

Literature review in February 2020.

An ongoing outbreak of pneumonia associated with a novel coronavirus was reported in Wuhan city, Hubei province, China. Affected patients were geographically linked with a local wet market as a potential source. No data on person-to-person or nosocomial transmission have been published to date.¹ In this study, we report the epidemiological, clinical, laboratory, radiological, and microbiological findings of five patients in a family cluster who presented with unexplained pneumonia after returning to Shenzhen, Guangdong province, China, after a visit to Wuhan, and an additional family member who did not travel to Wuhan. Phylogenetic analysis of genetic sequences from these patients were done.¹

From Jan 10, 2020, we enrolled a family of six patients who travelled to Wuhan from Shenzhen between Dec 29, 2019 and Jan 4, 2020. Of six family members who travelled to Wuhan, five were identified as infected with the novel coronavirus. Additionally, one family member, who did not travel to Wuhan, became infected with the virus after several days of contact with four of the family members. None of the family members had contacts with Wuhan markets or animals, although two had visited a Wuhan hospital. Five family members (aged 36–66 years) presented with fever, upper or lower respiratory tract symptoms, or diarrhoea, or a combination of these 3–6 days after exposure. They presented to our hospital (The University of Hong Kong-Shenzhen Hospital, Shenzhen) 6–10 days after symptom onset. They and one asymptomatic child (aged 10 years) had radiological ground-glass lung opacities. Older patients (aged >60 years) had more systemic symptoms, extensive radiological ground-glass lung changes, lymphopenia, thrombocytopenia, and increased C-reactive protein and lactate dehydrogenase levels. The nasopharyngeal or throat swabs of these six patients were negative for known respiratory microbes by point-of-care multiplex RT-PCR, but five patients (four adults and the child) were RT-PCR positive for genes encoding the internal RNA-dependent RNA polymerase and surface Spike protein of this novel coronavirus, which were confirmed by Sanger sequencing. Phylogenetic analysis of these five patients' RT-PCR amplicons and two full genomes by next-generation sequencing showed that this is a novel coronavirus, which is

closest to the bat severe acute respiratory syndrome (SARS)-related coronaviruses found in Chinese horseshoe bats.¹ Our findings are consistent with person-to-person transmission of this novel coronavirus in hospital and family settings, and the reports of infected travellers in other geographical regions.¹

A familial cluster of 5 patients with COVID-19 pneumonia in Anyang, China, had contact before their symptom onset with an asymptomatic family member who had traveled from the epidemic center of Wuhan. The sequence of events suggests that the coronavirus may have been transmitted by the asymptomatic carrier. The incubation period for patient 1 was 19 days, which is long but within the reported range of 0 to 24 days. Her first RT-PCR result was negative; false-negative results have been observed related to the quality of the kit, the collected sample, or performance of the test. RT-PCR has been widely deployed in diagnostic virology and has yielded few false-positive outcomes. Thus, her second RT-PCR result was unlikely to have been a false-positive and was used to define infection with the coronavirus that causes COVID-19.²

An outbreak of 2019 novel coronavirus diseases (COVID-19) in Wuhan, China has spread quickly nationwide. Here, we report results of a descriptive, exploratory analysis of all cases diagnosed as of February 11, 2020. All COVID-19 cases reported through February 11, 2020 were extracted from China's Infectious Disease Information System. Analyses included: 1) summary of patient characteristics; 2) examination of age distributions and sex ratios; 3) calculation of case fatality and mortality rates; 4) geo-temporal analysis of viral spread; 5) epidemiological curve construction; and 6) subgroup analysis. A total of 72 314 patient records-44 672 (61.8%) confirmed cases, 16 186 (22.4%) suspected cases, 10567 (14.6%) clinical diagnosed cases (Hubei only), and 889 asymptomatic cases (1.2%)-contributed data for the analysis. Among confirmed cases, most were aged 30-79 years (86.6%), diagnosed in Hubei (74.7%), and considered mild (80.9%). A total of 1 023 deaths occurred among confirmed cases for an overall case-fatality rate of 2.3%. The COVID-19 spread outward from Hubei sometime after December 2019 and by February 11, 2020, 1 386 counties across all 31 provinces were affected. The epidemic curve of onset of symptoms peaked in January 23-26, then began to decline leading up to February 11. A total of 1 716 health workers have become infected and 5 have died (0.3%). The COVID-19 epidemic has spread very quickly. It only took 30 days to expand from Hubei to the rest of Mainland China. With many people returning from a long holiday, China needs to prepare for the possible rebound of the epidemic.³

Over the past 20 years, several coronaviruses have crossed the species barrier into humans, causing outbreaks of severe, and often fatal, respiratory illness. Since SARS-CoV was first identified in animal markets, global viromics projects have discovered thousands of coronavirus sequences in diverse animals and geographic regions. Unfortunately, there are few tools available to functionally test these viruses for their ability to infect humans, which has severely hampered efforts to predict the next zoonotic viral outbreak. Here, we developed

an approach to rapidly screen lineage B betacoronaviruses, such as SARS-CoV and the recent SARS-CoV-2, for receptor usage and their ability to infect cell types from different species. We show that host protease processing during viral entry is a significant barrier for several lineage B viruses and that bypassing this barrier allows several lineage B viruses to enter human cells through an unknown receptor. We also demonstrate how different lineage B viruses can recombine to gain entry into human cells, and confirm that human ACE2 is the receptor for the recently emerging SARS-CoV-2.¹⁰

Emerging infectious diseases, such as severe acute respiratory syndrome (SARS) and Zika virus disease, present a major threat to public health. Despite intense research efforts, how, when and where new diseases appear are still a source of considerable uncertainty. A severe respiratory disease was recently reported in Wuhan, Hubei province, China. As of 25 January 2020, at least 1,975 cases had been reported since the first patient was hospitalized on 12 December 2019. Epidemiological investigations have suggested that the outbreak was associated with a seafood market in Wuhan. Here we study a single patient who was a worker at the market and who was admitted to the Central Hospital of Wuhan on 26 December 2019 while experiencing a severe respiratory syndrome that included fever, dizziness and a cough. Metagenomic RNA sequencing of a sample of bronchoalveolar lavage fluid from the patient identified a new RNA virus strain from the family *Coronaviridae*, which is designated here ‘WH-Human 1’ coronavirus (and has also been referred to as ‘2019-nCoV’). Phylogenetic analysis of the complete viral genome (29,903 nucleotides) revealed that the virus was most closely related (89.1% nucleotide similarity) to a group of SARS-like coronaviruses (genus Betacoronavirus, subgenus Sarbecovirus) that had previously been found in bats in China. This outbreak highlights the ongoing ability of viral spill-over from animals to cause severe disease in humans.¹¹

Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans. Here we report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Full-length genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of SARSr-CoV. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.¹²

Literature review in March 2020.

Since 2002, beta coronaviruses (CoV) have caused three zoonotic outbreaks, SARS-CoV in 2002–2003, MERS-CoV in 2012, and the newly emerged SARS-CoV-2 in late 2019. However, little is currently known about the biology of SARS-CoV-2. Here, using SARS-CoV-2 S protein pseudovirus system, we confirm that human angiotensin converting enzyme 2 (hACE2) is the receptor for SARS-CoV-2, find that SARS-CoV-2 enters 293/hACE2 cells mainly through endocytosis, that PIKfyve, TPC2, and cathepsin L are critical for entry, and that SARS-CoV-2 S protein is less stable than SARS-CoV S. Polyclonal anti-SARS S1 antibodies T62 inhibit entry of SARS-CoV S but not SARS-CoV-2 S pseudovirions. Further studies using recovered SARS and COVID-19 patients' sera show limited cross-neutralization, suggesting that recovery from one infection might not protect against the other. Our results present potential targets for development of drugs and vaccines for SARS-CoV-2. ⁴

As of 29 February 2020 there were 79,394 confirmed cases and 2,838 deaths from COVID-19 in mainland China. Of these, 48,557 cases and 2,169 deaths occurred in the epicenter, Wuhan. A key public health priority during the emergence of a novel pathogen is estimating clinical severity, which requires properly adjusting for the case ascertainment rate and the delay between symptoms onset and death. Using public and published information, we estimate that the overall symptomatic case fatality risk (the probability of dying after developing symptoms) of COVID-19 in Wuhan was 1.4% (0.9–2.1%), which is substantially lower than both the corresponding crude or naïve confirmed case fatality risk ($2,169/48,557 = 4.5\%$) and the approximator of deaths/deaths + recoveries ($2,169/2,169 + 17,572 = 11\%$) as of 29 February 2020. Compared to those aged 30–59 years, those aged below 30 and above 59 years were 0.6 (0.3–1.1) and 5.1 (4.2–6.1) times more likely to die after developing symptoms. The risk of symptomatic infection increased with age (for example, at ~4% per year among adults aged 30–60 years).⁵

Since the first reports of novel pneumonia (COVID-19) in Wuhan, Hubei province, China, there has been considerable discussion on the origin of the causative virus, SARS-CoV-2 (also referred to as HCoV-19). Infections with SARS-CoV-2 are now widespread, and as of 11 March 2020, 121,564 cases have been confirmed in more than 110 countries, with 4,373 deaths. SARS-CoV-2 is the seventh coronavirus known to infect humans; SARS-CoV, MERS-CoV and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43 and 229E are associated with mild symptoms. Here we review what can be deduced about the origin of SARS-CoV-2 from comparative analysis of genomic data. We offer a perspective on the notable features of the SARS-CoV-2 genome and discuss scenarios by which they could have arisen. Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus.⁶

Our comparison of alpha- and betacoronaviruses identifies two notable genomic features of SARS-CoV-2: (i) on the basis of structural studies and biochemical experiments, SARS-CoV-2 appears to be optimized for binding to the human receptor ACE2; and (ii) the spike protein of SARS-CoV-2 has a functional polybasic (furin) cleavage site at the S1–S2 boundary through the insertion of 12 nucleotides, which additionally led to the predicted acquisition of three O-linked glycans around the site. The receptor-binding domain (RBD) in the spike protein is the most variable part of the coronavirus genome. Six RBD amino acids have been shown to be critical for binding to ACE2 receptors and for determining the host range of SARS-CoV-like viruses. With coordinates based on SARS-CoV, they are Y442, L472, N479, D480, T487 and Y4911, which correspond to L455, F486, Q493, S494, N501 and Y505 in SARS-CoV-2. Five of these six residues differ between SARS-CoV-2 and SARS-CoV. On the basis of structural studies and biochemical experiments, SARS-CoV-2 seems to have an RBD that binds with high affinity to ACE2 from humans, ferrets, cats and other species with high receptor homology.⁷

The second notable feature of SARS-CoV-2 is a polybasic cleavage site (RRAR) at the junction of S1 and S2, the two subunits of the spike. This allows effective cleavage by furin and other proteases and has a role in determining viral infectivity and host range. In addition, a leading proline is also inserted at this site in SARS-CoV-2; thus, the inserted sequence is PRRA. The turn created by the proline is predicted to result in the addition of O-linked glycans to S673, T678 and S686, which flank the cleavage site and are unique to SARS-CoV-2. Polybasic cleavage sites have not been observed in related ‘lineage B’ betacoronaviruses, although other human betacoronaviruses, including HKU1 (lineage A), have those sites and predicted O-linked glycans. Given the level of genetic variation in the spike, it is likely that SARS-CoV-2-like viruses with partial or full polybasic cleavage sites will be discovered in other species.⁷

The functional consequence of the polybasic cleavage site in SARS-CoV-2 is unknown, and it will be important to determine its impact on transmissibility and pathogenesis in animal models. Experiments with SARS-CoV have shown that insertion of a furin cleavage site at the S1–S2 junction enhances cell–cell fusion without affecting viral entry. In addition, efficient cleavage of the MERS-CoV spike enables MERS-like coronaviruses from bats to infect human cells. In avian influenza viruses, rapid replication and transmission in highly dense chicken populations selects for the acquisition of polybasic cleavage sites in the hemagglutinin (HA) protein, which serves a function similar to that of the coronavirus spike protein. Acquisition of polybasic cleavage sites in HA, by insertion or recombination, converts low-pathogenicity avian influenza viruses into highly pathogenic forms. The acquisition of polybasic cleavage sites by HA has also been observed after repeated passage in cell culture or through animals.⁷

The function of the predicted O-linked glycans is unclear, but they could create a ‘mucin-like domain’ that shields epitopes or key residues on the SARS-CoV-2 spike protein. Several viruses utilize mucin-like domains as glycan shields involved immunoevasion. Although prediction of

O-linked glycosylation is robust, experimental studies are needed to determine if these sites are used in SARS-CoV-2.⁶

The authors report the kinetics of immune responses in relation to clinical and virological features of a patient with mild-to-moderate coronavirus disease 2019 (COVID-19) that required hospitalization. Increased antibody-secreting cells (ASCs), follicular helper T cells (TFH cells), activated CD4+ T cells and CD8+ T cells and immunoglobulin M (IgM) and IgG antibodies that bound the COVID-19-causing coronavirus SARS-CoV-2 were detected in blood before symptomatic recovery. These immunological changes persisted for at least 7 d following full resolution of symptoms.⁸

The outbreak of 2019-novel coronavirus disease (COVID-19) that is caused by SARS-CoV-2 has spread rapidly in China, and has developed to be a Public Health Emergency of International Concern. However, no specific antiviral treatments or vaccines are available yet. This work aims to share strategies and candidate antigens to develop safe and effective vaccines against SARS-CoV-2. The authors assume that virus-based vaccines should prove valuable in combatting COVID-19. In addition to the entire virus particle-associated inactivated or attenuated viral vaccines, the subunit candidates, such as S1 protein and/or the RBD element of SARS-CoV-2, are also valuable targets for vaccine design. Combining subunit vaccines with established or new adjuvants such as alum versus modern adjuvants such as the GSK AS series of adjuvants may represent a faster and safer strategy to move through early clinical development with the caveat that the protective efficacy may not be strong enough. As a result, immunizing the subunit vaccines with proper delivery platforms and immunization strategies to enhance the immune responses should be considered. We expect researchers who are racing against time will bring a new SARS-CoV-2-based vaccine from gene sequence to clinical testing in approximately 16–20 weeks.⁹

The human tendency to impose a single interpretation in ambiguous situations carries huge dangers in addressing COVID-19. We need to search actively for multiple interpretations, and governments need to choose policies that are robust if their preferred theory turns out to be wrong.¹³

In the current absence of medical treatment and vaccination, the unfolding COVID-19 pandemic can only be brought under control by massive and rapid behaviour change. To achieve this we need to systematically monitor and understand how different individuals perceive risk and what prompts them to act upon it.¹⁴

COVID-19's rapid move from warning sign to global pandemic has yanked the spotlight onto a number of questions humanity has been uneasily avoiding for years. Beyond the human-focused ones like how to keep a global economy running when flights are shut down, it has also drawn attention to the human exploitation of ecosystems as national assets, which

compels the human–animal interactions that probably made the virus infectious to humans in the first place. While scientists around the world are engaged in furious detective work (<https://www.nbcnews.com/science/science-news/where-did-new-coronavirus-come-past-outbreaks-provide-hints-n1144521>) and few concrete answers have emerged, it seems the virus was zoonotic: it jumped from animals to humans. The most likely suspect at the time this piece was written is bats. But while the virus is genetically similar to ones found in bats, those can't infect human cells. If the bat coronavirus is the source of the current outbreak, it must have mutated into its current form, probably via another animal. This transmitter animal is suspected to be the pangolin, a scaly anteater native to Asia and Africa. The pangolin is the world's most trafficked mammal (<https://www.bbc.com/news/science-environment-47200816>), highly sought after in China and other Asian countries for its meat, and especially for its scales, which are used in traditional medicine. Because of this demand it faces a real danger of extinction. The similarities between COVID-19 and pangolin-borne coronaviruses has focused attention on places where bats and pangolins may have spent time in close proximity. The most obvious suspect is the wildlife markets of Hubei, the Chinese province where the outbreak was first detected. The Chinese government has announced a 'comprehensive' ban on the trade and consumption (as food) of wildlife. This move has been praised by wildlife protection agencies worldwide, although many have pointed out that similar bans were quickly relaxed (<https://ewn.co.za/2020/02/24/china-comprehensively-bans-illegal-wildlife-trade>) after the SARS (severe acute respiratory syndrome) crisis in 2003.¹⁵

The year 2020 should have been the start of an exciting decade in medicine and science, with the development and maturation of several digital technologies that can be applied to tackle major clinical problems and diseases. These digital technologies include the internet of things (IoT) with next-generation telecommunication networks (e.g., 5G); big-data analytics; artificial intelligence (AI) that uses deep learning; and blockchain technology. They are highly inter-related: the proliferation of the IoT (e.g., devices and instruments) in hospitals and clinics facilitates the establishment of a highly interconnected digital ecosystem, enabling real-time data collection at scale, which could then be used by AI and deep learning systems to understand healthcare trends, model risk associations and predict outcomes. This is enhanced by blockchain technology, a back-linked database with cryptographic protocols and a network of distributed computers in different organizations, integrating peer-to-peer networks to ensure that data are copied in multiple physical locations, with modified algorithms to ensure data are secured but traceable.¹⁶

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes coronavirus disease 2019 (COVID-19), first emerged in China in December 2019 and has now spread worldwide, with a reported 351,731 confirmed cases and 15,374 deaths as of 23 March 2020 according to John Hopkins University. The infection is typically characterized by respiratory symptoms, which indicates droplet transmission. However, several case studies have reported gastrointestinal symptoms and/or evidence that some patients with SARS-CoV-

2 infection have viral RNA or live infectious virus present in faeces, which suggests that another possible route might be faecal–oral transmission. In a clinical characterization of ten paediatric patients with SARS-CoV-2 infection in China, none of whom required respiratory support or intensive care and all of whom lacked signs of pneumonia, eight tested positive on rectal swabs, even after nasopharyngeal testing was negative. The details were published as a Brief Communication in *Nature Medicine*. The patients, whose ages ranged from 2 months to 15 years, initially tested positive after being screened by nasopharyngeal swab real-time reverse transcription PCR (RT–PCR). Next, the researchers conducted a series of nasopharyngeal and rectal swabs to investigate the pattern of viral excretion. Eight patients had real-time RT–PCR-positive rectal swabs. In addition, these eight patients had persistently positive rectal swabs even after their nasopharyngeal tests were negative. Four patients were discharged after two consecutive negative rectal swabs, but the rectal swabs of two of these patients later became positive again, despite nasopharyngeal tests remaining negative. Finally, the researchers used the viral RNA measurements to determine that viral shedding from the digestive system might be longer-lasting than that from the respiratory tract. The findings suggest that we also need to use rectal swabs to confirm diagnosis of COVID-19, says Kang Zhang, a corresponding author of the study.¹⁷

Chloroquine — an approved malaria drug — is known in nanomedicine research for the investigation of nanoparticle uptake in cells, and may have potential for the treatment of COVID-19. Recent multicentre clinical trials¹ and cell culture studies² suggest that the 70-year-old malaria drug, chloroquine, may potentially display therapeutic efficacy against COVID-19 (corona virus disease 2019), a rapidly spreading viral infection that can cause pneumonia-induced death in approximately 2.5% of infected individuals^{1,3}. Based on the preliminary clinical trial findings, chloroquine has been included in federal guidelines for treatment of COVID-19 in the People’s Republic of China. However, caution should be exercised when making premature interpretations, as clinical trials are still ongoing and interim trial data have not yet been made available. Given the current lack of an approved and effective vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)¹, the virus causing COVID-19, it is important to evaluate potential prophylactic and/or therapeutic effects of drugs that are clinically approved for other indications. Chloroquine and its derivative, hydroxychloroquine, have a long history as safe and inexpensive drugs for use as prophylactic measures in malaria-endemic regions and as daily treatments for autoimmune diseases with the most common side effect being eye damage after long-term use⁴. Although previous studies have revealed that chloroquine has therapeutic activity against viruses⁵, including human coronavirus OC43 in animal models⁶ and SARS-CoV in cell culture studies⁷, anti-viral mechanisms of chloroquine remain speculative. Chloroquine has been used in the field of nanomedicine for the investigation of nanoparticle uptake in cells, and, therefore, insights from synthetic nanoparticle interactions with cells in the presence of chloroquine may reveal mechanisms that are active at early stages prior to viral replication. Specifically,

nanomedicine studies may provide clues on chloroquine-induced alterations of SARS-CoV-2 cellular uptake.¹⁸

Around 1 AM on Friday 28 January 2020, Nigeria announced sub-Saharan Africa's first confirmed case of the coronavirus disease COVID-19, and the confirmation led to activation of the country's National Coronavirus Emergency Operation Centre. Nigeria's quick mobilization of resources and manpower to combat the Ebola virus disease in 2014, led by the Nigeria Centre for Disease Control (NCDC), received praise from the international community and from the World Health Organization (WHO). The outbreak, which caused 15,000 confirmed cases and over 9,000 suspected cases in West Africa, was controlled in just 92 days—a "piece of world-class epidemiological detective work," the WHO stated at the time. This new coronavirus is putting the country's and the continents' recently expanded response infrastructure to the test. But Aderinola Olaolu, Deputy Incident Manager of Nigeria's Coronavirus Emergency Operation, notes that for COVID-19, the country had the time to prepare.¹⁹

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells through ACE2 receptors, leading to coronavirus disease (COVID-19)-related pneumonia, while also causing acute myocardial injury and chronic damage to the cardiovascular system. Therefore, particular attention should be given to cardiovascular protection during treatment for COVID-19.²⁰

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