Editorial

Considerations for future novel human-infecting coronavirus outbreaks

Georges Sinclair[1,2], Philippa Johnstone[3], Mustafa Aziz Hatiboglu[1]

[1]Department of Neurosurgery, Bezmialem Vakif University Medical School, Istanbul, Turkey, [2]Department of Oncology, North Middlesex University Hospital, London, United Kingdom, [3]Department of Oncology, Oxford University Hospitals NHS Trust, Churchill Hospital, Oxford, United Kingdom.

E-mail: Georges Sinclair - georges.sinclair@gmail.com; *Philippa Johnstone - philippa.johnstone1@nhs.net; Mustafa Aziz Hatiboglu - azizhatiboglu@yahoo.com

*Corresponding author:
Georges Sinclair,
Department of Neurosurgery,
Bezmialem Vakif University
Medical School, Istanbul,
Turkey; Department of
Oncology, North Middlesex
University Hospital, London,
United Kingdom.

georges.sinclair@gmail.com

ABSTRACT

Up until, June 13, 2020, >7,500,000 cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and >400,000 deaths, across 216 countries, have been confirmed by the World Health Organization (WHO). With reference to the two previous beta-CoV outbreaks (SARS-CoV and middle east respiratory syndrome [MERS]), this paper examines the pathophysiological and clinical similarities seen across all three CoVs, with a special interest in the neuroinvasive capability and subsequent consequences for patients with primary or metastatic brain tumors. More widely, we examine the lessons learned from the management of such large-scale crises in the past, specifically looking at the South Korean experience of MERS and the subsequent shift in disaster management response to SARS-CoV-2, based on prior knowledge gained. We assess the strategies with which infection prevention and control can, or perhaps should, be implemented to best contain the spread of such viruses in the event of a further likely outbreak in the future.

Keywords: Infection control and prevention, Middle East respiratory syndrome, Neuroinvasion, Severe acute respiratory syndrome coronavirus 2, Severe acute respiratory syndrome coronavirus

BACKGROUND

Up until, June 13, 2020, >7,500,000 cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and >400,000 deaths, across 216 countries, have been confirmed by the World Health Organization (WHO).[68] Numbers will most probably double within the next weeks to months ahead. As neuro-oncologists and neurosurgeons, we have been confronted with questions concerning the prevention, safety, and continuance of surgical and oncological treatments in the face of the SARS-CoV-2 pandemic. Our recommendations remain mainly based on national, regional, and local health-care policies;[57] many of which differ based on local demographics, societal behavior, and available resources. Despite a lower mortality rate,[51] SARS-CoV-2 has led to more fatalities than the previous two outbreaks of human-infecting beta-coronaviruses (Beta-CoV) combined (i.e., severe acute SARS-CoV and middle east respiratory syndrome [MERS]).[67,69] Elderly patients with extensive comorbidities are at higher risk of succumbing to the infection.[23] It is also reported that the risk of SARS-CoV-2 infection and death is increased in cancer patients.[3,57] Considering the potential of CoVs to deploy and replicate within the peripheral and the central nervous systems (CNSs),[40-43,49] it is only fair to assume that neuro-oncology patients are at high risk for serious SARS-CoV-2-associated complications, particularly those immune-compromised.

While SARS-CoV-2 associated disease (also known as coronavirus disease or COVID 19) continued to spreading in most continents, East-Asian countries were the first to bring hope, with reports of small numbers of confirmed cases and low fatality rate 3–4 months following the outbreak in China. [26,28,68] In view of the pathophysiological nature and evolution characteristics of CoV outbreaks seen over the past two decades as well as the numbers of therapeutic trials and related studies rapidly evolving,[19,64] we will most probably succeed in eventually containing this latest pandemic, yet at a staggering price in terms of fatalities, possible long-term physical and psychological sequelae in survivors (yet to be studied) as well as worldwide economic challenges.[34] Moreover, seldom have we seen such a degree of interest and source of debate within the medical community as the one caused by COVID-19. Indeed, reviewing the literature using the PubMed search engine (COVID 19 + SARS-CoV-2) we found 10,117 results on the subject, covering a broad spectrum of topics, from niche aspects of the virus to comprehensive reports. Some of our peers might regard a number of these works as mere repetitive papers, hence not worth considering. Yet bearing in mind the ravages in the health-care sector and the ensuing pernicious ramifications on world economy following the COVID-19 (despite its predecessors), there may never be a sufficient number of publications to help raise a warning flag about how poorly prepared most countries were. As such, two pertinent questions arise: what have we learned from this current outbreak? And, how will the next world outbreak be managed, particularly if confronted by a novel, more aggressive form of beta-CoV or any other viral agent behaving in a similar manner? Moreover, although we recognize the need of guidelines to balance the need for cardinal life-preserving treatments (surgery, radiation, and systemic treatment) with general anti-pandemic control measures, would these still be applicable to future outbreaks?[24] To answer the above questions and develop robust guidelines to help us better protect our patients, it is necessary to retrace the origin and stages of dissemination of SARS-CoV-2 in relation to the two beta-CoV predecessors (SARS-CoV and MERS), while understanding the pattern of behavior of these viral agents and the strategic steps necessary to successfully contain the number of infections and subsequent fatality rate. In the latter case, the South Korean response to SARS-CoV-2 has been an admirable example of a self-sufficient, prompt-acting infection control model, planned, and engineered to prevail at a time of global infection-related crisis. The intention of this paper is to highlight the above queries from a historical, pathophysiological, and strategic crisis management perspective.

COVS: THE "BASICS" IN RETROSPECT

The first human infecting CoV presenting with respiratory symptoms was reported in the Lancet as early as 1966 by Gosain *et al.*[19] In 1985, Berger presented serologic surveys on CoVs, indicating a worldwide presence while causing 1–35% of the upper respiratory infections depending on the seasons, mostly mild in character.[5] Today, we know that CoVs are enveloped, single-stranded, positive-sense RNA viruses, with a genome ranging from 26 to 32 kilobases in length.[22,47,51] Stratified into four separate genera (α–, β–, γ–, and δ-), CoVs are known for effectively utilizing several animal hosts, including camels, bats, masked palm civets, mice, dogs and cats, as well as different avian species; affected animals include both those found in the wild and those in domestic market places.[20,47] In this particular framework, the α– and β– CoV genera have a penchant for mammalian hosts, however, the γ– and, δ- CoVs for avian hosts.[23] To complicate matters further, evolving subtypes of mammalian CoVs are regularly being reported.[47] Animal-to-human and human-to-human vectorization is a common feature for CoVs;[20,48] however, there have been emerging reports of human-to-animal transmission, such as in the cases of kept domestic cats and dogs.[3] Fortunately, most human born CoVs have an indolent evolution, mimicking those of a common cold, such as in the case of the α-CoV subtypes HCoV-229E and HCoV-NL63, as well as the β-CoVs subtypes HCoV-HKU1 and HCoV-OC43.[23,47] Notwithstanding this, the world has been confronted to three separate human-infecting lethal outbreaks of β-CoV since 2002:[22,47,72]

1. The SARS-CoV

Emanating from an animal market in Guangdong (China), the virus spread to 37 countries, infecting >8000 persons; 774 casualties were reported between 2002 and 2003, setting the mortality rate at around 10%.[22,47] Human-to-human transmission was the principal form of spread, particularly through droplet exposure from expectoration, sneezing, handshakes, and contaminated surfaces.[22] ACE-2 receptors of the respiratory tract were identified as the prime target for cellular entry, using the receptor-binding domain (RBD) of the spike protein. Ultimately, the palm civet was identified as the intermediary host.[7,72] The predominant clinical traits of SARS-CoV included severe respiratory symptoms and acute kidney injury (AKI); severe neurologic and neuropsychiatric disorders were also described.[5,59] The nosocomial spread is also a main feature of SARS-CoV, with a high proportion of health-care staff becoming infected, for example, 22% and >40% in China and Canada, respectively.[72] A summary of the clinical characteristics of SARS-CoV is shown in [Table 1].[9,11,16,22,31,44,47,50,56,65,67,72]

2. The MERS-CoV

Initially identified in Saudi Arabia in 2012, this beta-CoV managed to spread to 27 countries.[4,69] Up to late January

Table 1: General characteristics of SARS-CoV, MERS, and SARS-CoV-2.[9,11,16,22,31,44,47,50,56,65,67,72]

	SARS-CoV	MERS	SARS-CoV 2
Country of origin	China	Saudi Arabia	China
Number of lab-confirmed cases	>8000	2538 (WHO, as per February 29, 2020)	>7,500,000 (WHO, as per June 13, 2020)
Number of fatalities	773	871 (WHO, as per February 29, 2020)	>400,000 (WHO, as per June 13, 2020)
Overall mortality rate	10%	35%	Still debated, app 3.5%
Total number of countries affected	37	27	216
Main cause of death	Respiratory distress	Respiratory distress	Respiratory distress
Mean incubation time (and 95% CI) in days	4.7 (4.3–5.1)	5.8 (5.0-6.5)	4.9 (4.4-5.5)
Main affected age group (primary infection) as per the WHO	Mainly those <50	50–59	43–66
Animal host			
Intermediary	Palm Civet	Camel	Market animals*
Of origin	Bats	Bats	Bats*
Receptors for cell access	ACE 2	DPP4	ACE 2
Cyto- and chemokines observed in the severe form of the disease	IL-1, IL-6, IL-8, IL-12, Interferon-gamma, CCL2, CXCL9, CXCL10	TNF-α, IL-6, CXCL-10, CCL-2, CCL-3, CCL-5, and IL-8	IL-2, (IL-6?) IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α. Macrophage Activation Syndrome-like disease (Cytokine Storm)
Susceptibility for nosocomial spread	Strong	Strong	Still unclear
Estimated R0	4	1	2.6–4.7
Reported potential for neuroinvasion in experimental studies	Yes	Yes	Potentially, in need of confirmation.
Genomic relation to SARS CoV2	70%	50%	-
Specific antiviral treatment	Not available (only symptomatic management)	Not available (only symptomatic management)	Not available (only symptomatic management)
Imaging (chest XR and CT-scan)	Unilateral lung changes (mostly), peripheral ground-glass opacities and/or consolidations. Seldom pneumothorax	Bilateral (80%) and unilateral (20%) lung changes with peripheral ground-glass opacities and/or consolidations. Pleural effusion can be present. Seldom pneumothorax	Bilateral, peripheral ground-glass opacities and/or consolidations. Seldom pneumothorax
Detection	Molecular and immunoassays	Molecular and immunoassays	Molecular and immunoassays
Lethal outcome associated to advanced age, comorbidities (including cancer)	Yes	Yes (stronger)	Yes (stronger)
Neurological and neuro-psychiatric disorders described	Yes	Yes	Yes

*Still to be confirmed by further studies

2020, the WHO confirmed a total of 2519 lab-confirmed cases of MERS along with 866 fatalities worldwide, >80% occurring in Saudi Arabia (2121 cases and 788 deaths).[69] Of interest, South Korea was the country most affected outside the Middle East, reporting a total of 38 casualties (2015);[22,47] this event was to prove pivotal in the way South Korean authorities would manage the current outbreak of SARS-CoV-2. Although the overall mortality rate of MERS has

been estimated at around 35%,[4,22,52] it has been seen to escalate to 60-70% in those needing mechanical ventilation.[4] Dromedary contact has been recognized as the main source of animal-to-human transmission.[7,52,72] As in the case of SARS-CoV, nosocomial contamination and "superspreaders" were major concerns, unfortunately, demonstrated in South Korea. Clinically, MERS leads to severe respiratory symptoms along with an AKI, and possible host immune deficiency

triggered by dipeptidyl peptidase 4-receptor cellular invasion (DPP4, also known as CD26). As with SARS-Co-V, severe forms of neurologic deficit and neuropsychiatric disorders have also been reported.[5,59] Interestingly, pre-existing chronic conditions such as diabetes, hypertension, kidney disease, and cardiopulmonary disease, were more frequently observed in patients with MERS than those affected by SARS-CoV.[72] A summary of these features is shown in Table 1.

3. The SARS-CoV-2

With its epicenter in the city of Wuhan (China), this novel form of human-infecting betaCoV was first reported in late December 2019.[23,35] In a retrospective study involving nine cases, Lu *et al.* (Feb 2020) reported that the genome sequence of the newly identified SARS-CoV-2 was 88% related to the CoVs bat-SL-CoVZC45 and bat-SL-CoVZXC21 (two bat-related CoVs from eastern China, first identified in 2018), 79% to SARS-CoV and 50% to MERS-CoV.[1,36,47] Much was brought to light by this study as well as by others to follow. First, bats seem to be the original host of SARS-CoV-2, although other concurrent reservoirs cannot be ruled out. [23,47] Second, as in the case of SARS-CoV, it may explain the propensity of SARS-CoV-2 (as in the case of SARS-CoV) to target ACE-2 receptors as a portal for cellular entry utilizing the RBD-domain of the spike protein. Third, it may account for the common ground and similarities shared by these three beta-CoVs, particularly, SARS-CoV and SARS-CoV-2 in terms of human-to-human transmission, particular mechanisms of dissemination (see below), symptoms, and radiological findings [Table 1]. As a novel beta-CoV, the environmental mechanisms implied in human transmission are yet to be fully understood; however, aerosolization and direct contact are widely recognized as precipitators of spread; some reports have cautiously suggested fecal, blood, and intra-uterine transmission as other forms of dissemination.[1,23,62,73] Although the overall mortality rate of SARS-CoV-2 remains a subject of debate within the scientific community (initially up to 5.2% across 204 countries),[58] it is considered lower compared to the previous two beta-CoV outbreaks.[4,22,47] Paradoxically, the death toll of SARS-CoV-2 is proving much higher in particular groups due to synchronous factors, including a stronger rate of contamination and reproduction, the presence of super-spreaders and societal driven comorbidity. Indeed, as presented by the scoping review of Adhikari *et al.*,[1] the R_0 (basic reproduction number, defined as the average number of secondary infectious cases produced by a single infectious case) of SARS-CoV-2 is believed to be 2.6–4.7[1,58] [Table 1]. The outcomes worsen with age (8% and 14% mortality for those 70–79 and >80 years of age, respectively),[71] particularly those with pre-existing comorbidities such as cardiovascular and pulmonary disease, diabetes, and cancer.[2,23] Of note, the latest estimates from the US Centers for Disease Control and

Prevention (CDC) are difficult to disregard; with an R_0 set at 2.5, the current best estimate for the infection fatality ratio is of 0.0065; in this setting, an estimated 40% of infections remain asymptomatic while transmission before symptom onset is believed to be as high as 50%.[8]

Although SARS-CoV-2 appears to affect male and female patients equally in numbers, the fatality rate is seemingly higher in men, possibly due to a difference in immunological responses surrogate to gender itself and gender-associated social behavior, such as smoking.[66] *In vivo* studies on SARS-CoV conducted by Channappanavar *et al.* seem to bring further support to the above.[9] Indeed, the authors reported that male mice were more susceptible to infection compared to age-matched females;[10] moreover, female mice subjected to ovariectomy or estrogen receptor antagonists presented an increased risk of succumbing to the infection, suggesting a protective role from estrogen receptor signal pathways.[10]

SARS-COV-2: FURTHER CLINICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

With an incubation time stretching from 1 to 14 days (commonly 3–7 days), the clinical management of SARS-Cov-2 remains structured on symptomatic care, dynamically hinging on the severity, and complexity of the clinical evolution. Non-neurologic symptoms from SARS-CoV-2 are often diffuse; pyrexia, shivers, fatigue, loss appetite, nasal congestion, sneezing, sore throat, cough, shortness of breath, nausea, vomiting, diarrhea, coagulopathies, skin rashes, and myalgia have been reported.[7,52] As with the previous CoV outbreaks, AKI is not uncommon. Mild-to-severe viral pneumonia with typical ground-glass changes seen on computed tomography,[25] acute respiratory distress syndrome (ARDS), and even sepsis with ensuing multi-organ dysfunction may evolve, particularly in elderly individuals (>70 of age) with underlying comorbidities.[7,71] Indeed, the severity of the disease seem to be linked to a macrophage activation syndrome (MAS)-like process, ultimately releasing an important number of pro-inflammatory cytokines, commonly called 'cytokine storm' [Table 1].

MAS, also known as secondary hemophagocytic lymphohistiocytosis, has been commonly linked to viral infections, autoimmune disorders, and malignancy; although the pathogenesis is still poorly understood, it is thought that the cytokine storm results in activation of macrophages, causing hemophagocytosis and contributing to disseminated intravascular coagulation, as well as contributing to multi-organ dysfunction.[15,32,50] For further details, we recommend the work of McGonagle *et al.*[50] on the subject. Notably, unless suffering from serious conditions, children seem to be less affected by SARS-CoV-2, developing at most mild symptoms.[17]

Finally, the differential diagnosis can include bacterial infections (e.g., *L. pneumophila,* and *S. pneumoniae*), other viral infections (rhinovirus, adenovirus, influenza, parainfluenza, human metapneumovirus, and respiratory syncytial virus) and other non-infectious etiology, such as malignancies, pulmonary embolism, vasculitis, and dermatomyositis.[7]

Ramifications of neurotropism

Of interest, neurological symptoms such as headaches, nausea, anosmia, loss of taste, acute cerebrovascular complications, diplopia, ataxia, seizures, drowsiness, consciousness deficit, depression, anxiety, delirium, posttraumatic stress, and cortisone-free subthreshold of mania have also been reported.[41,49] This is not entirely surprising as many CoVs are strongly associated to neuroinvasive activity;[41-43] the best example is the swine hemaglutinating encephalomyelitis virus (HEV). Closely related to SARS-CoV, this was the first reported beta-CoV able to penetrate the CNS. Using the epithelial lining of the respiratory tract and small intestines as their primary port of entry, HEVs are also capable of penetrating the CNS through retrograde peripheral nerve invasion; once established in the CNS, further dissemination by an inter-neuronal trans-synaptic exchange is carried out, mainly through membranous-coating-mediated endo- and exocytosis.[41-43] Interestingly, SARS-CoV and MERS-associated encephalopathy have previously been described,[5] indicating the capacity of the aforementioned viral agents to mimic these patterns of neuro-invasion;[41] indeed, although not frequent, psychiatric and neuropsychiatric presentation have been reported on all three human infecting CoVs.[59] Rogers *et al.* reported delirium as a common feature in the acute stage of SARS-CoV, MERS, and SARS-CoV2;[59] the authors also reported depression, anxiety, fatigue, and posttraumatic stress disorder in the post illness stage of SARS-CoV and MERS. Moreover, other studies on SARS-CoV suggest that this form of trans-synaptic activity is more palpable at the level of the cardiorespiratory center of the brainstem, yet originating at extracranial epicenters, such as the mechano- and chemoreceptors of the respiratory tract.[41-43] In this context, *in vivo* studies by Li *et al.* involving transgenic mice with human ACE-2 and DPP4 receptors are worth mentioning; following intranasal inoculation of SARS-COV-1 and MERS, both beta-CoVs were observed to disseminate into different areas of the brain, including the thalamus and brainstem; in this aspect, the olfactory nerves were thought to be the potential points of passage.[40,41] Furthermore, when inoculated at low concentrations, MERS-CoV particles were solely found in the brain and not at extracranial sites, suggesting the viral charge to be the cause of concurrent respiratory failure in mice.[40,41] Indeed, although cellular expression of ACE-2 and DPP4 receptors remains the principle gates of cellular entrance

for SARS-CoV-1 and MERS, respectively, their presence does not guarantee access to the targeted cells;[41] this is best reflected by cells with low or no receptor expression (such as hepatocytes or neural cells) found to host beta-CoVs.[41] Yet, further studies on SARS-CoV-2, including postmortem examinations, are necessary to elucidate the true role of the infection in neurological morbidity.

Therefore, in view of the genomic/phylogenetic, pathophysiological, and clinical traits shared among the above-mentioned human-infecting beta-CoVs, we hypothesize that, until proven otherwise, SARS-CoV-2 may well utilize similar mechanisms as those employed by MERS and SARS-CoV to effectively invade host neural cells and safely replicate in the CNS, ultimately leading to peripheral and central neurologic injury as well as extracranial symptomatology, including severe respiratory failure. Furthermore, considering the increased risk of COVID-19 in cancer patients,[2] it is only fair to hypothesize that, from a neuro-oncological perspective, patients with metastatic brain disease and/or malignant primary brain tumors are at high risk for lethal SARS-CoV2 infections, particularly those immunocompromised due to disease activity and/or active oncological treatment.

TREATMENTS AND TRIALS

Unfortunately, as pointed out above, there are no specific antiviral treatments or vaccines against SARS-CoV-2 at present; symptomatic care remains the foundation of hospital management. Oxygen therapy, continuous positive airways pressure (CPAP) support, and mechanical ventilation are effective at different stages of the infection, hinging on the degree of severity of respiratory problems; thorough guidelines and indications have been developed in the context of SARS-CoV-2-associated ARDS and can be found in more detail elsewhere.[7,54] The administration of intravenous steroids and antibiotics is recommended only in selected cases.[7,54] However, considering the rapid increase of symptomatic cases requiring advanced hospital assistance, some drugs have been used on symptomatic patients with lab-confirmed SARS-CoV-2, despite a lack of phase 3 trial evidence, including combined therapies such as Hydroxychloroquine + Azithromycine, Lopinavir+ Ritonavir, and Darunavir + Ritonavir and single agents such as alpha-interferon.[7,52] Interestingly, vitamins, minerals, and the herbal-based products have also been hypothesized to be effective treatments against SARS-CoV-2 infection, including Vitamin D_3,[21,27,29,61] high dose Vitamin C (ascorbic acid),[6,12] the combination of zinc with chloroquine/hydroxychloroquine,[70] and curcumin (extract from the Curcuma Longa, a plant belonging to the ginger family).[46]

Several SARS-CoV-2 trials are in pipeline across the US, Europe, and Asia, covering the fields of epidemiology, detection, treatment, and vaccination.[53] Over 200 studies

are recruiting or are active without recruitment.[53] Many of these studies include the use of the above-mentioned drugs as well as Colchicine, Remdesivir (Anti-Ebola RNA therapy), specific anti-influenza treatments (Favipiravir and Oseltamivir), anti-interleukin agents (Anakinra, Siltuximab, Sarilumab, and Tocilizumab), CAR-NK cells, stem cells, Tacrolimus/Methylprednisolone (anti-calcineurin exercise with ensuing decreased T-cell activity), Emapalumab (anti-interferon-gamma normally indicated in hemophagocytic lymphohistiocytosis but used in SARS-CoV-2 to fight hyperinflammation and respiratory distress), the BCG-vaccine, and Bevacizumab (Anti-VEGF, for severe respiratory distress as per study guidelines). The comprehensive review by Gosain *et al.* gives a good overview of the main ongoing trials [19]; the complete list can be found at the US National Library of Medicine (ClinicalTrials.gov).[53]

PREVENTION AND CONTROL OF SARS-COV-2: WHERE ARE WE TODAY?

Infection prevention and control (IPC) measures remain the cornerstone of SARS-Cov-2 management in many countries;[1] from a community perspective, the latter involves basic actions such as blocking expectoration and sneezes with arm and tissues, disposal of contaminated tissues, keeping unwashed hands away from the face, soap and alcohol-based gel hand sanitation, use of masks, distancing when mandatory, and avoidance of symptomatic (suspected) cases.[1] More drastic government measures have included the closure of schools, universities, places of work, public space, and even borders with ensuing travel restrictions, ultimately leading to regional, and national "lockdowns" with detrimental consequences to both local and national economies worldwide. In the context of nosocomial management, specific actions like the conversion of out- and inpatient units into exclusive SARS-CoV-2 care wards, while precluding access to surgical theatres and chemotherapy suites, for example, have been put into place, as illustrated by Hatiboglu and Sinclair.[24] Although the intended benefit of IPC is clear here, this has not been without significant repercussions to patients across most disciplines; surgical neuro-oncology has been no exception.[24]

Trying to understand the reasons as to how we failed to avoid the current situation remains complex from a geopolitical and world economics perspective. However, in the face of this type of outbreak, medical professionals across different disciplines have recognized the need for early measures such as (i) the systematic distribution and time-effective use of respiratory masks (e.g., FFP3 and N95 masks) and other personal protective equipment (PPE) for the directly exposed health-care staff, (ii) the sustainability of the medical supply chain, and (iii) the supply of equipment allowing non-invasive and invasive ventilation (such as oxygen supply, CPAP machines, and mechanical ventilators).

Furthermore, in view of the basic reproduction number of SARS-CoV-2 combined with factors such an aging population, restricted hospital resources (particularly in some Emergency departments and Intensive Care Units), and lack of specific anti-SARS-CoV-2 treatment (or vaccine), medical professionals stressed from the early stages of COVID-19, the need to bring the effective reproduction number <1 through unrestricted, "targeted" testing of all symptomatic cases. The benefits of upfront testing using the reverse transcriptase-polymerase chain reaction (RT-PCR) test on collected saliva and mucus samples have been widely documented;[7,45,47] indeed, through the synthesis of a double-stranded DNA molecule from the targeted RNA structure, portions of the genetic code of SARS-CoV-2 can be successfully identified and preserved.[7,18,47] This first-line testing is critical to (i) identify those infected, usually within 24 h, (ii) proceed with symptomatic treatment (hospitalization vs. self-isolation), and (iii) trace and identify contacts while applying prophylactic isolation where necessary.[73] The WHO-collaborating Foundation for Innovative New Diagnostics (FIND) provides a comprehensive list of available diagnostic RT-PCR-kits for SARS-CoV-2; more information can be found on their website.[18] To further consolidate the historical timeline of the infection outside the realm of RT-PCR testing, a second phase large-scale antibody (IgM – IgG) or antigen-detection testing would be of benefit to (i) understand the true extent of the spread at regional and national levels (particularly when lifting a lockdown) and (ii) identify those having acquired immunity, particularly healthcare workers needed in critical areas with persisting SARS-CoV-2 activity. These types of immunoassays are already available as listed by FIND;[18] some of these require uncomplicated sample collection (such as blood droplets) and provide rapid test results with acceptable specificity and time-dependent sensibility, such as in the case of Pharmact's detection device (Berlin, Germany).[18]

VALUABLE LESSONS FOR FUTURE OUTBREAKS: THE SOUTH KOREAN EXPERIENCE

Following the outbreak of SARS-CoV in China, South Korea implemented a series of restrictive measures, which ultimately led to three confirmed cases of SARS-CoV with no fatalities. Already then, the WHO acknowledged South Korea as a model nation for its effective fight against SARS-CoV.[39] However, in 2015, South Korea was confronted with an outbreak of the novel beta-CoV, MERS. As in SARS-CoV-2, the South Korean MERS propagation was strongly associated to "superspreaders." Indeed, the origin of the outbreak was traced back to a single patient exposing 28 others in an emergency room at the Samsung Medical Center in Seoul;[13,33] incredibly, 83% of all MERS

infections were traced to just 5 "superspreaders."[55] Overall, 186 lab-confirmed cases were reported, nearly all of which of nosocomial origin; 38 fatalities were reported and 16,993 individuals were isolated for 14 days to control the outbreak; the epidemic lasted for 2 months.[35,55]

From an early stage, experts identified a series of dysfunctions in terms of disaster management and communication capability; experts also recognized the importance of a short window between the identification of cases and the activation of control measures to restrain the spread of MERS or other agents with similar behavioral patterns.[2,55] Furthermore, despite the relatively low numbers of affected cases in terms of the overall population, the economic loss was estimated at a staggering 8.5 billion US dollars.[55] The MERS outbreak changed the landscape of the South Korean medical system, structuring a nationwide strategy of preparedness for infectious diseases.[30,38,55] Indeed, factors such as the absence of expert resources, inadequate infection control infrastructure, and insufficient organized preparedness led the authorities to invest and restructure the health-care system.[55] Furthermore, as early as 2018, groups like Myong-do *et al*. recognized the need for international cooperation to fight these life-threatening infectious diseases;[55] the dramatic outcome of this outbreak has proved them right.[14,63]

On January 20, 2020, the first individual with SARS-CoV-2 was identified in South Korea; the number of cases rapidly increased during the following few weeks, with its epicenter in Daegu.[60] With 2,500,000 inhabitants, the city is located only 150 miles from the capital, Seoul (25,000,000 inhabitants); epidemiologically, the outbreak was traced back to a church community with "superspreading" activity (>4000 cases as of March 8, 2020); nosocomial transmission was the second source of spread (118 cases of which nine were medical staff as of March 8, 2020).[60] Most clusters were of local origin.[60]

In terms of governmental action, after confirming their first case, the South Korean authorities escalated the crisis level from blue to yellow, establishing a Korean CDC COVID-19 rapid response team. A week later (January 27), the crisis level was further elevated to orange, and the Ministry of Health and Welfare Central Accident Management Headquarters for the COVID-19 was established.[14] Government ministries rapidly coordinated several actions aiming to contain the SARS-CoV-2 outbreak.[14] Indeed, barely a month after the first reported case of SARS-CoV-2, a number of restrictive actions on public transportation, school activities, and social gatherings were activated, as well as enforcing preventive measures to counteract nosocomial spread. Governmental transparency, crisis readiness, conceived health-care resources, prompt testing of symptomatic individuals, systematic contact tracing, isolation, and civic awareness were key factors in the fight against SARS-CoV-2.[14,53,60]

In addition to the above, the benefits of incorporating cutting edge technology to public control measures cannot be underestimated; for example, from an early stage, the South Korean Ministry of Interior and Safety developed a smartphone application (app) to allow those infected or in isolation to keep in contact with case workers with positive results, allowing local authorities to keep track of "superspreaders," among others. Another app, the "Co100," was also rapidly developed from governmental data to inform users when they come within 100 m of a site visited by someone infected. Alike the latter mentioned apps, a third app was produced to specifically inform citizens of possible shortage and supply of masks at specific sites such as pharmacies.

Finally, despite South Korea's proximity to China and not launching a total "lockdown" as in the case of many European countries, the WHO and South Korean authorities have reported a sustained, stable number of infected cases with low fatality cases following the escalation and implementation of these measures (12,051 confirmed cases and 277 deaths up to June 13, despite a population >50,000,000); similar results in Taiwan, Japan, Singapore, and Germany further support an approach comparable to that seen in South Korea.[26]

CONCLUSION

This is the third outbreak by a novel human-infecting beta-CoVs in 18 years, with worldwide consequences; this should be taken as sign of warning, as it unlikely to be the last. SARS-CoV, MERS, and SARS-CoV-2 all share common and complex clinical, genomic, and pathophysiologic characteristics with potentially lethal outcomes. Of these three aforementioned CoVs, SARS-CoV-2 has the highest mortality rate due to an inherent high R_0 value and an ability to master both animal-to-animal and animal-to-human transmission. Due to several factors, not least including a lack of current targeted treatment, infection control, and preventive measures remain the cornerstone of the management of these types of agents. As proven by the South Korean model, prompt, large-scale testing of suspected individuals, contact tracing and isolation are critical steps in early crisis management aiming to avoid irrational 'full' lockdown measures with ensuing detrimental outcomes in the short- and long term. As such, transparent international cooperation between governments and health-institutions based on strict guidelines and obligatory crisis-oriented health-care resources ought to be implemented to prevent further global crises related to novel infectious agents.[37]

REFERENCES

1. Adhikari SP, Meng S, Wu Y, Mao YP, Ye RX, Wang QZ, *et al*. Epidemiology, causes, clinical manifestation and diagnosis,

prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infect Dis Poverty 2020;9:29.

2. Almendros A. Can companion animals become infected with Covid-19? Vet Rec 2020;186:388-9.

3. Al-Shamsi HO, Alhazzani W, Alhuraiji A, Coomes EA, Chemaly RF, Almuhanna M, *et al.* A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: An international collaborative group. Oncologist 2020;25:e936-45.

4. Alsolamy S, Arabi YM. Infection with Middle East respiratory syndrome coronavirus. Can J Respir Ther 2015;51:102.

5. Berger JR. COVID-19 and the nervous system. J Neurovirol 2020;26:143-8.

6. Carr AC. A new clinical trial to test high-dose Vitamin C in patients with COVID-19. Crit Care 2020;24:133.

7. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). Treasure Island, FL: Stat Pearls Publishing; 2020.

8. Centers for Disease Control and Prevention. COVID-19 Pandemic Planning Scenarios; 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html. [Last accessed on 2020 Jul 10].

9. Channappanavar R, Fett C, Mack M, Eyck PP, Meyerholz DK, Perlman S. Sex-based differences in susceptibility to SARS-CoV infection. J Immunol 2017;198:4046-53.

10. Chan-Yeung M, Xu RH. SARS: Epidemiology. Respirology 2003;8 Suppl 1:S9-14.

11. Chen X, Chughtai AA, Dyda A, MacIntyre CR. Comparative epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia and South Korea. Emerg Microbes Infect 2017;6:e51

12. Cheng RZ. Can early and high intravenous dose of Vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Med Drug Discov 2020;5:100028.

13. Cho SY, Kang JM, Ha YE, Park GE, Lee JY, Ko JH, *et al.* MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: An epidemiological outbreak study. Lancet 2016;388:994-1001.

14. COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention. Early epidemiological and clinical characteristics of 28 Cases of coronavirus disease in South Korea. Osong Public Health Res Perspect 2020;11:8-14.

15. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. Front Immunol 2019;10:119.

16. Development Finance Bureau at Ministry of Economy and Finance. Tackling COVID-19: Health, Quarantine and Economic Measures of South Korea. New Delhi: Ministry of Economy and Finance; 2020. Available from: https://www.eena.org/wp-content/uploads/tackling-covid-19.pdf. [Last accessed on 2020 Apr 16].

17. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, *et al.* Epidemiology of COVID-19 among children in China. Pediatrics 2020;145:e20200702.

18. Foundation for Innovative New Diagnostics. FIND Evaluation Update: SARS-CO-2 Molecular Diagnostics. Geneva: FIND; 2020. Available from: https://www.finddx.org/covid-19/sarscov2-eval-molecular. [Last accessed on 2020 Apr 16].

19. Gosain R, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff M. COVID-19 and cancer: A comprehensive review. Curr Oncol Rep 2020;22:53.

20. Gralinski L, Menachery V. Return of the coronavirus: 2019-nCoV. Viruses 2020;12:135.

21. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, *et al.* Evidence that Vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020;12:988.

22. Guarner J. Three emerging coronaviruses in two decades. Am J Clin Pathol 2020;153:420-1.

23. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, *et al.* The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. Mil Med Res 2020;7:11.

24. Hatiboglu MA, Sinclair G. Coronavirus pandemic: How is neurosurgical-oncology practice affected? Br J Neurosurg 2020; https://doi.org/10.1080/02688697.2020.1773398.

25. Hosseiny M, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology perspective of coronavirus disease 2019 (COVID-19): Lessons from severe acute respiratory syndrome and Middle East respiratory syndrome. AJR Am J Roentgenol 2020;214:1078-82.

26. Hsih WH, Cheng MY, Ho MW, Chou CH, Lin PC, Chi CY, *et al.* Featuring COVID-19 cases via screening symptomatic patients with epidemiologic link during flu season in a medical center of Central Taiwan. J Microbiol Immunol Infect 2020;53:459-66.

27. Ilie PC, Stefanescu S, Smith L. The role of Vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020;32:1195-8.

28. Iwasaki A and Grubaugh ND. Why does Japan have so few cases of COVID-19? EMBO Mol Med 2020;12:e12481.

29. Jakovac H. COVID-19 and vitamin D-is there a link and an opportunity for intervention? Am J Physiol Endocrinol Metab 2020;318:E589.

30. Jeon MH, Kim TH. Institutional preparedness to prevent future Middle East respiratory syndrome coronavirus-like outbreaks in republic of Korea. Infect Chemother 2016;48:75-80.

31. Jiang X, Rayner S, Luo MH. Does SARS-CoV-2 has a longer incubation period than SARS and MERS? J Med Virol 2020;92:476-8.

32. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: A distinct entity leading to early death in Sepsis. Front Immunol 2019;10:55.

33. Khan A, Farooqui A, Guan Y, Kelvin DJ. Lessons to learn from MERS-CoV outbreak in South Korea. J Infect Dev Ctries 2015;9:543-6.

34. Kickbusch I, Leung GM, Bhutta ZA, Matsoso MP, Ihekweazu C, Abbasi K. Covid-19: How a virus is turning the world upside down. BMJ 2020;369:m1336.

35. Kim KH, Tandi TE, Choi JW, Moon JM, Kim MS. Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: Epidemiology, characteristics and public health implications. J Hosp Infect 2017;95:207-13.

36. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:105924.

37. Lau SK, Chan JF. Coronaviruses: Emerging and re-emerging pathogens in humans and animals. Virol J 2015;12:209.

38. Lee J, Rapid Response Team, Kim WJ. Collaborative intervention of Middle East respiratory syndrome: Rapid response team. Infect Chemother 2016;48:71-4.

39. Lee KM, Jung K. Factors influencing the response to infectious diseases: Focusing on the case of SARS and MERS in South Korea. Int J Environ Res Public Health 2019;16:1432.

40. Li K, Wohlford-Lenane C, Perlman S, Zhao J, Jewell AK, Reznikov LR, *et al.* Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J Infect Dis 2016;213:712-22.

41. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020;92:552-5.

42. Li YC, Bai WZ, Hirano N, Hayashida T, Hashikawa T. Coronavirus infection of rat dorsal root ganglia: Ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. Virus Res 2012;163:628-35.

43. Li YC, Bai WZ, Hirano N, Hayashida T, Taniguchi T, Sugita Y, *et al.* Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. J Comp Neurol 2013;521:203-12.

44. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, *et al.* Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020;92:491-4.

45. Liu R, Han H, Liu F, Lv Z, Wu K, Liu Y, *et al.* Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 Cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin Chim Acta 2020;505:172-5.

46. Liu Z, Ying Y. The inhibitory effect of curcumin on virus-induced cytokine storm and its potential use in the associated severe pneumonia. Front Cell Dev Biol 2020;8:479.

47. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020;395:565-74.

48. Malik YS, Sircar S, Bhat S, Sharun K, Dhama K, Dadar M. Emerging novel coronavirus (2019-nCoV)-current scenario, evolutionary perspective based on genome analysis and recent developments. Vet Q 2020;40:68-76.

49. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, *et al.* Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: A retrospective case series study. Med Rxiv 2020; https://doi.org/10.1101/2020.02.22.20026500.

50. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020;19:102537.

51. Memish Z, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. Lancet 2020;395:1063-77.

52. Meo SA, Alhowikan AM, Al-Khlaiwi T, Meo IM, Halepoto DM, Iqbal M, *et al.* Novel coronavirus 2019-nCoV: Prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur Rev Med Pharmacol Sci 2020;24:2012-9.

53. National Institutes of Health: US National Library of Medicine; 2020. Available from: https://www.clinicaltrials.gov /ct2/results?cond=COVID+19&term= &cntry=&state=&city=&dist=. [Last accessed on 2020 Apr 06].

54. Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondi A, Palmieri F, *et al.* National institute for the infectious diseases L. Spallanzani IRCCS. Recommendations for COVID-19 clinical management. Infect Dis Rep 2020;12:8543.

55. Oh MD, Park WB, Park SW, Choe PG, Bang JH, Song K, *et al.* Middle East respiratory syndrome: What we learned from the 2015 outbreak in the Republic of Korea. Korean J Intern Med 2018;33:233-46.

56. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, *et al.* Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA 2020;323:1-9.

57. Patel R, Park J, Shah A, Saif MW. COVID-19 and cancer patients. Cancer Med J 2020;3:40-8.

58. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, *et al.* Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. Lancet Respir Med 2020;8:506-17.

59. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, *et al.* Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020;7:611-27.

60. Shim E, Tariq A, Choi W, Lee Y, Chowell G. Transmission potential and severity of COVID 19 in South Korea. Int J Infect Dis 2020;93:339-44.

61. Silberstein M. Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19? Med Hypotheses 2020;140:109767.

62. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 2020;87:281-6.

63. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, *et al.* World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020;76:71-6.

64. Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, *et al.* COVID-19: A promising cure for the global panic. Sci Total Environ 2020;725:138277.

65. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol 2020;92:568-76.

66. Wenham C, Smith J, Morgan R, Gender and COVID-19 Working Group. COVID-19: The gendered impacts of the outbreak. Lancet 2020;395:846-8.

67. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report-77. Geneva: World Health Organization; 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200406-sitrep-77-covid-19.pdf?sfvrsn=21d1e632_2. [Last accessed on 2020 Apr 06].

68. World Health Organization. Middle East Respiratory

Syndrome: MERS Situation. Geneva: World Health Organization; 2020. Available from: http://www.emro.who.int/health-topics/mers-cov/mers-outbreaks.html. [Last accessed on 2020 Jun 15].]

69. World Health Organization: Severe Acute Respiratory Syndrome (SARS) Epidemiology Working Group. Consensus Document on the Epidemiology of Severe Acute Respiratory Syndrome (SARS). Department of Communicable Disease Surveillance and Prevention. Geneva: World Health Organization; 2020. Available from: https://www.who.int/csr/sars/en/whoconsensus.pdf. [Last accessed on 2020 Apr 16].

70. Wu R, Wang L, Kuo HD, Shannar A, Peter R, Chou PJ, *et al.* An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep 2020;1-15. Doi: 10.1007/s40495-020-00216-7.

71. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 Cases from the Chinese center for disease control and prevention. JAMA 2020;323:1239-42.

72. Yin Y, Wunderink R. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology 2018;23:130-7.

73. Zhang T, Cui X, Zhao X, Wang J, Zheng J, Zheng G, *et al.* Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia. Med Virol 2020;92:909-14.