Editorial

Considerations for future novel human-infecting coronavirus outbreaks

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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).[66] 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,[157] 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.[22] 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. [26,28,48] 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, [12,47,51] 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.[17] 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.[21,47] 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, handshake, 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. [7,70] The predominant clinical traits of SARS-CoV included severe respiratory symptoms and acute kidney injury (AKI); severe neurologic and neuropsychiatric disorders were also described.[3,58] 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. [4,49] Up to late January
of MERS along with 866 fatalities worldwide, >80% occurring in Saudi Arabia (2121 cases and 788 deaths). Of interest, South Korea was the country most affected outside the Middle East, reporting a total of 38 casualties (2015); 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%, it has been seen to escalate to 60-70% in those needing mechanical ventilation. Dromedary contact has been recognized as the main source of animal-to-human transmission. 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.

| Table 1: General characteristics of SARS-CoV, MERS, and SARS-CoV-2. |
|---------------------------------|-----------------|-----------------|
| **Country of origin**          | SARS-CoV         | MERS            | SARS-CoV 2   |
| **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% |
| **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**                | Palm Civet      | Camel           | Market animals* |
| **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 neuropsychiatric disorders described** | Yes | Yes | Yes |

*Still to be confirmed by further studies
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.[1,26,47] 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 R₀ (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.[15,58] [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 R₀ set at 2.5, the current best estimate for the infection fatality ratio is 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.[8] 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.[7,21] 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.[80] 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. [40-43] 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-CoV-2; [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, [58] 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. [7,44] The administration of intravenous steroids and antibiotics is recommended only in selected cases. [7,44] 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 + Azithromycin, Lopinavir+Ritonavir, and Darunavir + Ritonavir and single agents such as alpha-interferon. [7,22] Interestingly, vitamins, minerals, and the herbal-based products have also been hypothesized to be effective treatments against SARS-CoV-2 infection, including Vitamin D₃ [21,27,29,61] high dose Vitamin C (ascorbic acid), [8,12] the combination of zinc with chloroquine/hydroxychloroquine, [79] 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

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are recruiting or are active without recruitment.\[19\] 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).\[19\]

**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;\[11\] 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.\[19\] 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,\[31,33\] incredibly, 83% of all MERS
Infections were traced to just 5 "superspreaders."
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.\[55\]

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.\[13,55\] 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.\[16,38,55\] 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 Myongdo et al. recognized the need for international cooperation to fight these life-threatening infectious diseases;\[15\] 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.\[14,33,60\]

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. Like 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.\[37\]

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