SARS-CoV-2 Therapy: Old Drugs as New Interventions

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Abstract: An outburst of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a grave threat to global health and the economy. As of May 13, 2020, a total of 42,81,838 cases have been confirmed, with over 2,92,376 deaths worldwide. In India, 75,048 cases have been reported to date with 2,440 deaths. Management of this new coronavirus (COVID19) has mainly focused on infection prevention, case detection, monitoring, and supportive care. As there is no vaccine or specific antiviral treatment for human SARS-CoV-2, therefore identifying the drug treatment options as soon as possible is critical for the response to the COVID19 outbreak. Pro-inflammatory cascade and cytokine storm play a key role in the pathogenesis of new coronavirus. A large number of therapeutic interventions such as antiviral, antimalarial, convalescent plasma therapy, BCG vaccine, mTOR inhibitors, Tissue Plasminogen Activator, Human monoclonal antibodies, Anti-parasitic agents, Immunoen- hancers, Nutritional interventions, JAK-STAT signaling inhibitors, ACE2 receptor modulators, and Angiotensin II receptor blockers have been either tried or suggested for effective treatment of patients with SARS-CoV-2 disease. Hence, we recommend that all the above potential interventions must be implemented in terms of their safety and efficacy through proper clinical experiments to control the emerging SARS-CoV-2 disease.

Keywords: SARS-CoV-2, ACE2 receptor modulators, cytokine storm, antimalarial, immunoenhancers, mTOR inhibitors, JAK-STAT signaling inhibitors.

1. INTRODUCTION

A newly emerged human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially reported in Wuhan, China, has become a chief concern all over the world. On 30 January 2020, the World Health Organization (WHO) officially declared the SARS-CoV-2 (previously known as COVID-19) epidemic as a global public health emergency. The blowout of COVID-19 reached epidemic proportions in China and has also been found in 184 other countries. To date, 42,81,838 cases have been confirmed, with over 2,92,376 deaths worldwide. In India, 75,048 cases have been reported to date with 2,440 deaths [1]. Coronaviruses were first defined in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds [2]. SARS-CoV-2 is a member of betacoronavirus similar to SARS-CoV. The genome of SARS-CoV-2 is large (∼30-kb) single-stranded, positive-sense ribonu- cleic acid (RNA) genome packed inside a nucleocapsid protein, surrounded by an envelope. The SARS-CoV-2 genome encodes non-structural proteins (i.e., 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (spike glycoprotein) and accessory proteins [2, 18, 19]. The spike protein consists
of S1 and S2 subunits, respectively [4, 19, 20]. It has been reported that a minimal receptor-binding domain (RBD) is located in the S1 subunit and consists of the receptor-binding motif (RBM), which may facilitate the virus-cell receptor [angiotensin-converting enzyme 2 (ACE2)] interaction [3, 21-23]. Recent findings show that the sequence of COVID-19 (RBM) that directly acquaintances the ACE2 receptor is similar to that of SARS-CoV and reveals that 2019-nCoV (Wuhan) uses ACE2 as its receptor [3]. Therefore, the spike protein (s) may be a potential target for preventive measures from COVID19. Further, the clinical symptoms of COVID-19 patients include fever, cough, and fatigue. A small population of patients may also likely face gastrointestinal infection symptoms [10, 13, 24]. Early pathogenesis of SARS-CoV includes the activation of the immune system (dendritic cells macrophages and neutrophils). These immune cells further express a battery of pro-inflammatory cytokines and chemokines including interleukin 1β (IL-1β), IL-2, IL-6, IL-8, interferon (IFN-α,β, and γ) Tumor Necrosis Factor (TNF), CeC motif chemokine 3 (CCL3), CCL5, CCL2, interferon-inducible protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1) [25, 26]. Interleukin-6 (IL-6) is an imperative member of the cytokine network, which plays a central role as a pro-inflammatory mediator. The main activators of IL-6 expression are IL-1β, and tumor necrosis factor (TNF-α). In the preliminary stage of infectious inflammation, IL-6 plays a central role in stimulating various host cell defense mechanisms [27]. Unfortunately, the overproduction of these cytokines and chemokines also may contribute to a pathological condition termed as “Cytokine storm” [28]. Based on genetic homology and pathologic features of the infected lung, some clinical studies consider cytokine storm to be one of the major causes of disease aggravation in critical patients like increase in vascular permeability, accumulation of a large number of fluid and blood cells into the alveoli, resulting in dyspnea and even respiratory failure [29-34]. Therefore, suppression of the cytokine storm is an effective way to prevent the deterioration of patients suffering from COVID-19 infection (Fig. 1). Moreover, based on an immune response, a recent study has assumed the clinical phase to be divided into three district phases: 1. the viremia phase, 2. the acute phase (pneumonia phase), and the 3. recovery phase. If the immune function of patients in the acute phase (pneumonia phase) is intact, the virus can be effectively suppressed and then can enter the recovery phase. If the patient is older, or in an immune-compromised state, combined with other basic diseases such as hypertension and diabetes, the immune system cannot effectively control the virus in the acute phase (pneumonia phase), causing the patient to some severe or critical type [35].

According to WHO, the management of COVID-19 has mainly focused on infection prevention, case detection, and monitoring, and supportive care. Until now, no vaccine or specific antiviral treatment is available to treat human COVID-19 infection. As new chemical entities are likely to require months to years to develop. Meanwhile, given the urgency of the COVID-19 outbreak, we focus here on the potential to repurpose existing drugs such as antiviral (Favilavir, Sofosbuvir, Ribavirin, Remdisivir, and Lopinavir/Ritonavir), antimalarial (Chloroquine, hydroxychloroquine, and Mefloquine), convalescent plasma therapy, BCG vaccine, mTOR inhibitors (sirolimus, everolimus or temsirolimus), Tissue Plasminogen Activator, Human monoclonal antibodies (Tocilizumab), Anti-parasitic agents (Ivermectin), Immunomodulators (Interferons), Nutritional interventions (Vitamins A, C, D and minerals like zinc and selenium), JAK-STAT signaling inhibitors (Baricitinib, Fedratinib, and Ruxolitinib), ACE2 receptor modulators (Nicotiamine, flavonoids), and Angiotensin II receptor blockers (Losartan) to control or prevent emerging infections of COVID-19 outbreak.

2. POTENTIAL THERAPEUTIC INTERVENTIONS FOR SARS-COV-2

2.1. Antiviral Agents

RNA-dependent RNA polymerase (RdRp) is a crucial enzyme in the life cycle of RNA viruses. RdRp is a potential therapeutic target in different RNA viruses, including coronaviruses [4]. Several in vitro and clinical trials have been started in China for RdRp selective inhibitors such as Favilavir, Sofosbuvir, Ribavirin against RdRp to target new strain of coronavirus. Results depicted that Sofosbuvir, Ribavirin, and Remdisivir can be significantly effective against the new strain of coronavirus [4, 36]. Besides, Remdesivir may be a novel potential drug for the treatment of COVID19. Pre-clinical experiments have shown that compared with the control group, Remdesivir could effectively reduce the virus titer of mice infected with MERS, decrease the lung tissue injury, and its effect is restored in comparison to Lopinavir/Ritonavir combined with interferon-β [21, 37]. However, double-blind and randomized controlled trials are still required to determine the safety and efficacy of remdesivir. In other studies, evidence about the effectiveness of repurposed lopinavir/ritonavir against SARS and the Middle East Respiratory Syndrome (MERS) coronavirus (CoV), as well as preliminary docking studies conducted by the ICMR-National Institute of Virology, Pune, the Central Drugs Standard Control Organization approved the restricted public health use of lopinavir/ritonavir combination amongst symptomatic COVID-19 patients detected in the country [38-40]. A recent in vitro study has also shown that the combination of Lopinavir with litonavir, was able to suppress coronavirus replication to a certain extent [41]. Therefore, the above antiviral drugs are potential entities and can be evaluated clinically to target COVID19 (Fig. 1).

2.2. Convalescent Plasma Therapy

Convalescent plasma is the plasma that is collected from recovered individuals, following the resolution of infection and the development of antibodies. Convalescent plasma products have been used to treat a variety of infectious diseases from earlier times. It has been used for the Severe Acute Respiratory Syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections [42, 43]. Previous reports have depicted that recovery plasma therapy may reduce the mortality rate of severe influenza A and SARS-CoV infection patients [41, 44]. Therefore, the safety and efficacy of convalescent plasma therapy should be
tested in SARS-CoV-2-infected patients as per the FDA permission [45] (Fig. 1).

2.3. Antimalarial Drugs

For very long-time Chloroquine (CQ) and Hydroxychloroquine (HCQ) have been assigned for prophylaxis and curative measure of malaria and autoimmune diseases such as lupus or rheumatoid arthritis worldwide [46-50]. Besides, their adverse effects are well-defined and can be severe, from neurological conditions to cardiac arrhythmia and sudden death [51, 52]. Chloroquine and 4-aminoquinoline drug hydroxychloroquine belong to the same molecular family. Hydroxychloroquine differs from chloroquine by the presence of a hydroxyl group at the end of the side chain: The N-ethyl substituent is β-hydroxylated. Interestingly, hydroxychloroquine has rapid gastrointestinal absorption and renal elimination to that of chloroquine. A recent finding has demonstrated that Chloroquine can be effective in vitro against the novel coronavirus SARS-CoV-2 (in Vero E6 cells) with an effective concentration of 50% (EC50) of 1.1 µM and EC90 of 6.9 µM [53, 54]. In a clinical study, chloroquine phosphate has demonstrated marked efficacy in the treatment of COVID-19 with few severe adverse reactions in more than 100 patients by shortening hospital stay [53]. Similarly, hydroxychloroquine has also demonstrated in vitro antiviral activity against SARS-CoV-2 with EC50 of 0.72 µM [55]. The advantage with hydroxychloroquine over chloroquine is that former drug can be used in high doses for long periods with very good tolerance [56]. Chloroquine and hydroxychloroquine seem to inhibit the fusion of the virus to the cell membrane by modulation of the endosomal pH. These drugs can also inhibit nucleic acid replication [57]. A recent report has mentioned the possible interventions of chloroquine on the replication cycle of SARS-CoV-2. Chloroquine and hydroxychloroquine may interfere with host ACE2 receptor glycosylation, thus preventing the virus binding to the target cell [58]. Furthermore, the drugs may also limit the biosynthesis of sialic acids that may be an essential component for cell surface binding of SARS-CoV-2 [59]. If the binding of some viral particles is achieved, these drugs may modulate the acidification of endosomes, thereby inhibiting the formation of the autophagosome [60]. Through the reduction of cellular mitogen-activated protein (MAP) kinase activation, chloroquine may also inhibit virus replication. In addition,
chloroquine may alter M protein maturation and interfere with virion assembly and budding [56]. Based on several clinical trials carried out in China to investigate the efficacy and safety of chloroquine and hydroxychloroquine, it has been recommended for COVID-19 patients to be treated with chloroquine phosphate at a dose of 500 mg twice per day for ten days [53, 61]. Interestingly, some reports show that the combination of Hydroxychloroquine (HCQ) or Chloroquine (CQ) with broad-spectrum macrolide antibiotic Azithromycin (AZ) has shown promising results in the treatment of COVID-19 patients [62-65]. A recently published report in nature has reported that both HCQ and AZ have been individually reported to elevate the risk of QT-interval prolongation, drug-induced torsades de pointes (a form of polymorphic ventricular tachycardia) and drug-induced sudden cardiac death [66-70]. Therefore, it is suggested to monitor the QTc repeatedly in COVID-19 patients who are treated with HY/AZ, predominantly in those with co-morbidities [71]. On the other hand, chloroquine is contraindicated in patients with severe renal or hepatic diseases [56]. Mefloquine (MFQ), another antimalarial drug, was found to have antiviral activity against both MERS-CoV and SARS-CoV. A recent study identified three clinically approved drugs chloroquine phosphate and hydroxychloroquine exhibited total attenuation of cytopathic effects in cell culture at 10 μmol/L. The study further suggests that these drugs should be considered for clinical trials in COVID-19 patients [72] (Fig. 1). The antiviral mechanisms of these three drugs are not completely understood. However, it has been proposed that CEP and mefloquine are likely to target host cell pathways, while selamectin might be a 2019-nCoV specific inhibitor [72].

2.4. BCG Vaccination

Bacillus Calmette-Guerin (BCG) is the live attenuated strain of Mycobacterium Bovis used as a vaccine for tuberculosis (TB) globally, including India, Japan, and China, having a universal BCG vaccination policy in newborns [73, 74]. There are some reports to suggest that BCG vaccination significantly increases the secretion of pro-inflammatory cytokines, specifically IL-6, IL-1β, and TNFα which have shown to play a vital role in adaptive antiviral immunity [75-77]. Interestingly, some reports depicted that children vaccinated with BCG were observed to have a significant decrease in overall mortality, which was accredited to its effect on reducing respiratory infections and sepsis [73, 78]. Further, it has been reported that the acquired immunity induced after vaccination of children can stimulate immunity against the SARS-CoV-2 virus [79-81]. Moreover, clinical trials of the BCG vaccine are urgently needed to establish its beneficial role in COVID-19, as suggested by the epidemiological data, especially in countries without a universal BCG vaccination policy (Fig. 1).

2.5. mTOR inhibitors

Cross-reactive antibodies-associated Antibody-Dependent Enhancement (ADE) may attribute to be one of the major causes of cytokine storm induced critical illness and death due to COVID-19 [82]. These cross-reactive antibodies are self-sufficient in delivering the virus to the Fc receptor of dendritic cells, after which, a huge number of viruses are replicated and released outside the cells after the immune escape fostering ADE [83, 84]. The inhibition of the activation of these memory B cells in elderly persons at an early stage of COVID-19, the ADE can be avoided, and severe symptoms can be prevented. The Mammalian Target of Rapamycin (mTOR) inhibitors can suppress cytokine storm early B-cell production in germinal centres and may inhibit such conditions [82]. Therefore, it is suggested to conduct a randomized, double-blind clinical trial to urgently confirm the safety and effectiveness of mTOR inhibitors, i.e., sirolimus, everolimus, or temsirolimus in the prevention of COVID-19 severity (Fig. 1).

2.6. Tissue Plasminogen Activator (tPA) Treatment

In the pathogenesis of Acute Respiratory Distress Syndrome (ARDS), besides the deposition of fibrin in the airspaces and lung parenchyma, fibrin-platelet microthrombi in the pulmonary vasculature takes place, which contributes to the development of progressive respiratory dysfunction SARS-CoV-2 patients [85]. The mechanism underlying is the dissolution of the extensive fibrin burden in the microcirculation and airway spaces in ARDS [86]. Therefore, targeting the coagulation and fibrinolytic approach through tPA can be a promising approach for the treatment of ARDS. However, a multicenter group from the USA had suggested that tPA could be an invaluable tool to reduce severe ARDS related to SARS-CoV-2 and act as a salvage technique to rescue patients when mechanical ventilation was not available and for patients who are eligible for salvage use therapeutics [87-89]. Therefore, tPA may be an effective therapy in patients with SARS-CoV-2-induced ARDS who have a pO2/FiO2 ratio of less than 60 and a PCO2 greater than 60 despite prone positioning and maximal mechanical ventilatory support, particularly in settings where extracorporeal membrane oxygenation (ECMO) is not a possibility (Fig. 1).

2.7. Human Monoclonal Antibodies

IL-6 is a multi-effective cytokine that plays a central role in anti-inflammatory and pro-inflammatory reactions and immune response [90]. IL-6 can be produced by almost all forms of immune cells. IL-6 binds to its receptor IL-6R to form a complex to initiate intracellular signal transduction. The most recent clinical studies suggested that IL-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms. Tocilizumab (TCZ), mainly used to treat rheumatoid arthritis, possess an antagonistic effect against IL-6 receptors [91]. Further, a recent single centered clinical study on COVID19 patients reported that a single dose of TCZ along with glucocorticoid was not able to improve the symptomatic relief in critically ill patients. However, repeated doses (even repeated with a lower dose) of TCZ might improve the condition of critically ill patients (Fig. 1). Therefore, as per safety advantage, a repeated dose of TCZ is more likely to be effective than glucocorticoid in the treatment of COVID-19 [92]. Apart from this, in a recently published study, a human monoclonal antibody has been reported to neutralize SARS-CoV-2 in cell culture by targeting a communal epitope on these viruses [93]. There-
fore, a clinical trial should be organized to study the safety and efficacy of this cross-neutralizing antibody in humans.

2.8. Anti-Parasitic Agents (Ivermectin)

Ivermectin is an FDA-approved broad-spectrum anti-parasitic agent that has shown to have antiviral activity against a broad spectrum of viruses in vitro. A recent report has shown that ivermectin can inhibit SARS-CoV-2, with a single addition in vitro [94]. Therefore, immediate clinical trials should be conducted to evaluate its possible therapeutic effects in humans against COVID19 (Fig. 1).

2.9. Immunoenhancers

Interferons (IFNs) is a large family of numerous type I species (IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω) and one type II species (IFN-γ) [95]. They act as a broad-spectrum antiviral agent through interaction with toll-like receptors and inhibit viral replication. Interferon-alfa and beta both demonstrated an anti-SARS-CoV activity in vitro [96, 97]. To date, the clinical effect of IFN intervention in COVID-19 infection is ambiguous. IFN-α showed in vitro inhibitory effects on SARS-CoV at concentrations of 1000 IU/ml [98]. In addition to their antiviral activity, IFNs show an immunomodulatory capability. Type I interferons can enhance natural killer (NK)-cell cytotoxicity, enhance the expression of major histocompatibility complex I proteins, and promote IFN production and the proliferation of NK cells and macrophages. A combination of interferon-α-2a, along with ribavirin, improved the survival of the patients with severe MERS-CoV infection [98] (Fig. 1). Therefore, these drugs can be a suitable candidate and can be employed to treat COVID-19 infection. However, more clinical trials are needed to establish their safety and efficacy.

2.10. Nutritional Interventions

2.10.1. Vitamins (A, C, D)

Vitamins and minerals from natural and dietary sources can help boost the immune system, which is an important component in fighting against viral infections. Therefore, these can be used as adjuvant therapy or a protective measure in COVID-19 prevention and treatment. It has been reported that vitamin A supplementation reduces morbidity and mortality in different infectious and life-threatening diseases, such as measles, diarrheal disease, measles-related pneumonia, Human Immunodeficiency Virus (HIV) infection, and malaria [99]. A previous report has shown that low vitamin A diet can reduce the efficacy of bovine coronavirus vaccines [100]. Therefore, vitamin A can play a promising role as adjuvant therapy in the treatment of SARS-CoV-2 and the prevention of lung infection. Further, it has been suggested that Vitamin C may function as a weak antihistamine agent, which may be helpful in providing relief from lower respiratory tract infections (flu-like symptoms). A previous randomized, clinical controlled trial revealed that there was a markedly lower incidence of pneumonia in vitamin C-supplemented groups, indicating that vitamin C might prevent the susceptibility to lower respiratory tract infections under certain conditions [101]. Therefore, vitamin C could be one of the effective candidates for the treatment of COVID-19. Similarly, Vitamin D (D3) has many mechanisms by which it reduces the risk of microbial infection and death. In addition to its role in preserving bone integrity, vitamin D3 metabolite 1α,25-dihydroxy vitamin D3 (1,25-(OH)2D3) is also a modulator of adaptive immunity by stimulating the maturation of monocyte, neutrophil and dendritic like immune cells [102]. In some preclinical studies, vitamin D reduced influenza A virus replication of rotavirus both in vitro and in vivo by another process [103, 104]. Vitamin D also enhances cellular immunity, in part by reducing the cytokine storm, which is one of the important pathological conditions in COVID19 [103]. Therefore, vitamin D may be used as a supplement to treat COVID19 (Fig. 1).

2.10.2. Minerals

Selenium is an essential trace element that plays a vital role in reactive oxygen species (ROS) homeostasis and redox regulation in the host cell [105]. Therefore, dietary selenium deficiency can alter a viral genome in such a way that a mild pathogenic virus can act as a highly virulent in the deficient host under oxidative stress [106, 107]. The deficit in selenium also induces not only impairment of the host immune system, but also a rapid transformation of benign variants of RNA viruses to virulence [108, 109]. Therefore, selenium supplementation can be an effective adjuvant therapy to treat this novel virus of COVID-19. Similarly, zinc is a dietary trace mineral supplement and is important for growth, development, and the maintenance of immune function of both the innate and adaptive immune system. Therefore, Zinc deficiency results in the dysfunctioning of the immune system and increases the susceptibility of the host to infectious diseases. It is also a component of nutritional immunity. By increasing the intracellular concentration zinc with zinc- ionophores like pyrithione can efficiently impair the replication of a variety of RNA viruses [110]. Besides, the combination of zinc and pyrithione at low concentrations inhibits the replication of SARS coronavirus. Therefore, Zn may possess a protective effect as preventive and adjuvant therapy of COVID-19 through reducing inflammation, improvement of mucociliary clearance, prevention of ventilator-induced lung injury, modulation of antiviral and antibacterial immunity [111]. Therefore, zinc supplements may have an effect not only on COVID-19-related symptoms like diarrhea and lower respiratory tract infection but also on COVID-19 itself (Fig. 1).

2.11. Jak-Stat Signaling Inhibitors

Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis and can reduce viral infection in vitro [3] (Fig. 1). All three are powerful anti-inflammatories that, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed in people with COVID-19 [44].

2.12. ACE2 Receptor Modulators

ACE2 receptors are extensively expressed on epithelial cells of alveoli, tracheobronchial tree, and may help virus entry [112]. Nicotianamine is an important metal-ligand in
plants, and it has been reported as a novel angiotensin-converting enzyme-2 inhibitor in soybean [113]. Interestingly, it can be a potential option to be used to reduce the infection of COVID-19. Citrus fruits are rich in flavonoids and are clinically documented to be helpful in relieving cough and can also promote digestive health. Therefore, citrus fruits are presumed to possess antivirus activities and enhance host immunity [114] (Fig. 1). A previous study has reported that hesperetin, a major component of citrus fruits, could act as a highly potent inhibitor of SARS-CoV 3CLpro [115].

2.13. Angiotensin II Receptor Blockers (ARB)

Recently, it has been documented that the serum level of angiotensin II (AngII) is significantly improved in COVID-19 patients and reveals a positive linear correlation to viral load and lung injury. Activation of the RAS can cause widespread endothelial dysfunction and varying degrees of multiple organs (heart, kidney, and lung) injuries. A preclinical study carried out in a mice model, who were infected with H5N1 influenza and further treated with ARB (Losartan), improved survival [116]. Thus, the intake of ARBs might probably relieve lung injury and decrease heart and renal damage, followed by COVID19 (Fig. 1). A recent study has hypothesized that people using losartan or telmisartan (ARB) as antihypertensives get fewer attacks of colds and flu-like illnesses [3]. Therefore, we suggest that a randomized clinical study should be performed further to establish the therapeutic role of ARBs in COVID19.

CONCLUSION

With the ongoing efforts to avert the spread of COVID19, we hope that social distancing and proper sensitization can play a defensive role in this pandemic worldwide. Above all repurposed treatment, we potentially suggest the use of convalescent plasma therapy concerning its safety and efficacy and cost-effective procedure of isolation mainly in developing countries where very limited resources are available for health. Apart from this, adequate nutrition can boost the immune response that may lead to fighting against several viral and bacterial infections. Therefore, we recommend verifying the nutritional status of COVID-19 infected patients before the administration of general treatments. Meanwhile, learning from previous experience in coping with SARS and MERS, a series of existing drugs have been tested, while some other drugs to be clinically tested for their efficacy and safety on humans to treat COVID-19 are ongoing. In the present review, we summarize all the potential interventions for COVID-19 infection according to previous treatments of SARS and MERS. Finally, with the ongoing efforts for the development of vaccines and novel therapeutic drugs to prevent the spread of COVID-19 worldwide, we hope that the outbreak may subside in a few months, as with SARS and MERS.

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