

EDITORIAL

COVID-19 in Qatar: Ways forward in public health and treatment

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INTRODUCTION

The rapid and virulent spread of new corona virus COVID-19 took many by surprise. It is a stark reminder of our constant battle with nature. COVID-19 has a diverse range of clinical presentations, and for individuals, the effects range from being asymptomatic to having viral pneumonitis and death. This editorial outlines (a) the underlying nature of COVID-19; (b) key public health measures and (c) some of the lessons learnt from other countries around the world.

EPIDEMIOLOGY OF COVID-19 IN QATAR

For many people in Qatar, they only experience mild and asymptomatic illness. A recent study suggested that as many as 78% of people with coronavirus have no symptoms. We also know that transmission rates are high in pre-symptomatic individuals [1]. At the time of writing (29/6/2020) Qatar had 94,413 confirmed cases of COVID-19 and 110 deaths. Worldwide, the equivalent figures were over ten million cases and half a million deaths [2]. Globally, Qatar has the highest prevalence of 33,872 cases per 1 million population, with a mortality rate of 4 per 100,000 [3]. At the same time only a small proportion of the population (3.4%) has been infected with COVID-19, and it appears the epidemiological curve is beginning to flatten.

CORONAVIRUS GENOME AND STRUCTURE: POTENTIAL IMPLICATIONS

Coronaviruses (CoV) constitute a single-stranded positive sense RNA genome of 26–32 kb length and have an outer protein envelop and spiky spherical surface [4]. The viral genome of the CoV encodes several structural proteins that help in entering, replicating and assembling virions in host cells, among them the spike 'protein S' is crucial for pathogenesis as it mediates

attachment to host cells. A report of five patients hospitalized with pneumonia in December 2019 showed that the viral genome sequencing of these patients have identified a novel strain of coronavirus [5].

To date there are four identified genera of coronavirus including MERS (Middle East respiratory syndrome) and SARS (severe acute respiratory syndromes) [6]. This virus shows 88% sequence homology with two bat-derived SARS-like coronaviruses, and about 50% sequence identity with MERS [7]. This new virus was first named "SARS-CoV-2" by the International Virus Classification Commission.

The fundamental role of the spike protein in infectivity suggests that it is a potential target for vaccine development, antibody-mediated blocking therapy and development of antigen-based diagnostic tests. In addition, some have suggested that multiplication of the SARS-CoV-2 genome relies on the viral RNA-dependent RNA polymerase which is another probable target for the investigational nucleotide analogue Remdesivir that has broad-spectrum antiviral activity against RNA viruses [8]. Therefore, the possible utilization of existing antiviral treatments has many advantages in terms of safety and efficacy to be administered as investigational drugs for novel SARS-CoV-2 infection.

Testing can be for antibodies or for the virus itself (viral or antigenic tests). The former is linked to developing herd immunity, the latter would perhaps be more appropriate for contact tracing.

PREVENTION AND PROPHYLAXIS

Prophylaxis

Currently there is no drug which is approved to be prescribed as a preexposure prophylaxis for COVID-19. Clinical trials on the antimalarial drugs hydroxychloroquine or chloroquine and HIV protease inhibitors are under investigation for prophylactic use. In April 2020 the Indian Council of Medical Research recommended chemoprophylaxis with hydroxychloroquine 400 mg taken twice on the first day followed by 400 mg once a week for asymptomatic healthcare workers in direct contact of confirmed or suspected COVID-19 patients, and for asymptomatic household contacts of confirmed cases. However Rathi et al., reminded us that the safety of these immunomodulators in people at risk of COVID-19 has never been evaluated [9].

Clinical trials and potential candidates of future drugs for COVID-19

To date there is no treatment that has been proved to be highly effective and safe against COVID-19. However, a number of drugs have shown some promising results in clinical trials such as: remdesivir, chloroquine or hydroxychloroquine, combination of lopinavir and ritonavir with or without interferon-beta-1a, azithromycin and a variety of traditional Chinese medicine products [10]. An open label Phase III randomized multi-country clinical trial known as "Solidarity trial of treatments for COVID-19

1. local standard of care plus injection Remdesivir daily infusion for 10 days.
2. local standard of care plus oral Lopinavir and Ritonavir twice daily for 14 days.
3. local standard of care plus oral Lopinavir and Ritonavir twice daily for 14 days with injection Interferon beta-1a for 6 days.
4. local standard of care plus oral Chloroquine or hydroxychloroquine two oral loading doses, then orally twice daily for 10 days.
5. local standard therapy alone = control group.

Figure 1. Five arms in Solidarity trial.

infection in hospitalized patients" (ISRCTN83971151) has been initiated in April 2020 by the WHO and recruits patients across 100 countries including Qatar, see [Figure 1](#) [11,12].

Remdesivir: (developed as GS-5734) It is a broad-spectrum antiviral drug and it was found to be effective in minimizing the lung damage in rhesus monkeys from MERS [13]. Remdesivir is a prodrug it gets converted to its active metabolite adenosine triphosphate which acts by inhibiting the RNA dependent RNA polymerase enzyme. It was found that it interrupts with the chain termination in Ebola virus. This drug was also found to be promising for the treatment of human immunodeficiency virus (HIV) type 1 and the hepatitis B virus [14,15]. On May 1, 2020 the US FDA issued an emergency use approval for remdesivir to treat laboratory confirmed cases of COVID-19 in children and adults and for patients with the severe form of the disease [16,8].

In a double-blinded, randomized, placebo-controlled trial of remdesivir on 1063 patients at a loading dose of 200 mg on the first day which was followed by 100 mg daily for up to 9 additional days has shown that it could shorten the recovery time in hospitalized COVID-19 patients [17].

Hydroxychloroquine (ATC Code: P01BA02) and Chloroquine (ATC Code: P01BA01): Chloroquine is a blood schizonticide, acts on the erythrocytic cycle of plasmodium species and has been used for malaria, rheumatoid arthritis over decades. It has got additional anti-inflammatory, immunomodulatory, local irritant and local anaesthetic, minor smooth muscle relaxant, antihistaminic and antiarrhythmic properties. Hydroxychloroquine, is similar to chloroquine but it is N-ethyl substituents of chloroquine. Hydroxychloroquine is FDA approved for treating lupus erythematosus [18,19]. An observational study in New York City concluded that hydroxychloroquine has not reduced intubation or death in patients with COVID-19. [20] Hydroxychloroquine and chloroquine are drugs which are extensively undergoing clinical trials worldwide and are part of the Solidarity trial, which was initiated by the WHO. In June 2020, the hydroxychloroquine arm of the Solidarity trial ([Figure 1](#)) was stopped as interim trial results showed that it produced little reduction in the mortality of hospitalized COVID-19 patients when compared to standard care [21].

Lopinavir – Ritonavir (ATC Code: J05AR10):

Lopinavir – ritonavir are both protease inhibitors used in the treatment of HIV. Lopinavir is structurally similar to ritonavir but is more potent [22]. Both antiretroviral drugs bind avidly with the SARS-CoV 3C-like protease (SARS-CoV 3CLpro) [23]. In a randomized controlled trial published in *New England Journal of Medicine* and conducted in China on lopinavir and ritonavir on 199 COVID-19 patients, it showed that there was no clinical benefit of the combination of drugs but there were more adverse effects e.g., nausea, vomiting and diarrhoea (Chinese Clinical Trial Register number, ChiCTR2000029308) [24].

Interferon beta-1a: (ATC Code: L03AB07) Is found to be effective in the treatment of multiple sclerosis [25]. Interferons are glycoprotein cytokines produced by host cells in response to viral infections. They have antiviral property and inhibit viruses in multiple steps, namely, viral penetration, synthesis of viral mRNA, assembly of viral particles and their release, suppression of viral protein synthesis. Interferon receptors are JAK-STAT tyrosine protein kinase receptors which on activation migrate to the nucleus and induce transcription of interferon-induced-proteins which exert antiviral effects. In a study conducted on MERS in Saudi Arabia, it was found that remdesivir and interferon beta have superior antiviral activity to lopinavir-ritonavir in vitro [26]. Combination of lopinavir – ritonavir and Interferon beta-1a was shown to be effective in patients infected with SARS and MERS in a transgenic humanized mouse model [27].

Other drugs which have shown promising results in clinical trials for COVID-19 are dexamethasone, azithromycin and fevipafavir.

Dexamethasone

Dexamethasone is a long acting corticosteroid with a half-life of > 36 hours. It is a known drug used for allergic reactions, cerebral oedema and shock. It was found to be very effective in COVID-19 patients in reducing mortality. The Recovery trial, which is one of the world's largest clinical trials has reported on June 16, 2020 that patients on dexamethasone 6 mg per day for 10 days has dramatically reduced the mortality in COVID-19 patients on ventilators. The case fatality rate was reduced by 20%. The probable mechanism by which dexamethasone is effective in patients with COVID-19 is by immunosuppressant

effects as an overactive immune system is manifested in COVID-19 patients [28].

Azithromycin

Azithromycin is a macrolide antibiotic. The mechanism of action against COVID-19 is still unknown. According to Poschet et al., azithromycin may increase the pH of endosomal cells preventing the entry, replication and spread of the virus [29]. Azithromycin also has anti-inflammatory and immunomodulatory effects reducing the pro-inflammatory state induced by COVID-19 [30–31]. A study on 1061 patients in France has shown that a combination of azithromycin and hydroxychloroquine is effective in COVID-19 treatment and is associated with a very low fatality rate in patients [32].

Favipavir

It is a broad spectrum inhibitor of viral RNA polymerase enzyme which is commonly used in the treatment of arenaviruses, bunyaviruses and filoviruses found to be effective in COVID-19 patients in mild to moderate symptoms of COVID-19 in India. Recently, favipavir was included in a phase 2 clinical trial [NCT04434248]. In a non-randomized trial of 80 patients with COVID-19 in China there was a reduction in the time to COVID-19 viral clearance in patients treated with favipavir compared with the lopinavir-ritonavir combination [33].

COVID-19 AND QATAR'S HEALTH SYSTEM

Qatar followed the WHO's global advice to all countries in mid-March: "test, test, and test". Qatar started testing early [34] and has now tested over 10% of its population. In terms of public health, antibody tests are important in detecting infections in people who are asymptomatic, and the more tests that are conducted the easier it becomes to trace (potentially) infected people to reduce transmission. The Qatar Ministry of Public Health [35] developed a framework for action identifying four key stages: (1) Preparedness, not just of the health services; (2) Surveillance and detection to ensure the earliest diagnosis, support and surveillance to contain outbreaks; (3) Response and containment to limit COVID-19 spread and ensure health services can provide high quality care to large numbers of severe patients, and (4) Recovery and continuity, especially mitigating socio-economic impacts, learn lessons and enhance future response capabilities.

As the proportion of tested people is higher in Qatar compared than in most other countries, so is the proportion of asymptomatic cases testing positive in the general population. The question is can Qatar cope? Does it have the capacity to test just under 3 million people and do the contact tracing?

In terms of health facilities, key questions in the 'Response & Containment' stage must address the following: Does Qatar have adequate bed capacity especially to deal with people affected by COVID-19 who are in need of ventilators in ICU? What is the availability of PPE (personal protective equipment) such as aprons, gloves, surgical masks and eye protection?

In terms of its health system, Qatar's Framework for Action followed the 2016 WHO *Guidelines on Core Components of Infection Prevention and Control (IPC) Programmes at the National and Acute Health Care Facility Level* [35]. Thus the Framework for Action includes cross-cutting programmes, such as: (1) Infection prevention and control in among frontline health workers at risk, (2) Communication strategy, and (3) Promoting COVID-19 research [36]. The latter includes Qatar participating in the already mentioned Solidarity trial [11–12].

STOPPING THE SPREAD OF COVID-19

In a global crisis there are both global and local factors at play. One key local factor in Qatar is its large migrant workers' population. Living and working conditions of migrant workers, such as camps are overcrowded. Qatar recognises the risk of infection in migrant workers, in addition to the importance of recording new cases of COVID-19 across the country. Whilst new infections have also increased among citizens and residents, as a result of contact with infected family members, who had been infected at work or family gatherings, suggests a lack of compliance of precautionary measures (Figure 2), especially physical distancing and staying at home. The ministry reports that (most) newly infected cases have been quarantined where they are receiving the necessary medical care [37].

It is important that any health promotion advice and regulations are made available in the key languages (such as Hindi, Bangla, Nepali) languages of Qatar's migrant workers as many do not speak Arabic or (poor) English. It is worthwhile asking the question: "What can Qatar learn from countries where COVID-19 appeared earlier". We highlight three examples below.

1. All citizens/residents to install tracing app 'Ehteraz'.
2. Max 2 people in one vehicle (3 for some exceptions).
3. Some sport allowed in areas close to residence, but with social distancing and face masks and avoiding gatherings from 19 May.
4. Closing shops and commercial activities 19-30 May, except food and catering shops, pharmacies and restaurant deliveries.

Figure 2. Qatar Public Health rules around COVID-19.

The UK started with a public health strategy referred to as 'flattening the epidemic curve' (Figure 1) and in the process building up a population-level 'herd immunity', while seeking to protect high-risk groups and hoping of the appearance of a vaccine and effective treatments in due course. This strategy did not include testing people suspected of having the virus but promotes self-isolation and improved hygiene measures as a personal prevention strategy.

India introduced a public health strategy based on severe measures to restrict movement of people to suppress the epidemic, a so-called lockdown. This involved mass quarantine, travel restrictions, closures of education establishments and workplaces, and so on, but not testing and contact tracing. This strategy is potentially better at preventing the spread of the virus in the short term, but it is not sustainable and is not easily tolerated for longer periods of time by many 'healthy' people.

South Korea acted fast in January 2020, having had experience from recent outbreaks of MERS. It had a strategy that involved a focus on testing and of tracing contacts of infected people. Testing and contact tracing is commonly used in other infectious diseases, such as sexually transmitted infections (STIs). Some countries did not prioritise testing to detect infected people followed by tracing others they had been in contact with, partly because it is less effective than for example partner tracing in STIs as COVID-19 can be transmitted by asymptomatic and pre-symptomatic individuals, and partly because the number of people a person with COVID-19 has contact with in a day is typically much higher than those related to sexual contacts.

REMOTE CARE THROUGH TELEHEALTH

The measures adopted internationally to curb the spread of COVID-19 have led to significant changes in how healthcare is accessed and provided. As face-to-face consultations between healthcare workers and patients pose a potential risk to both parties, remote care and telehealth offer alternatives.

Telehealth (or telemedicine) means providing personalised healthcare over a distance [38], it includes consultations and communication by phone, text messages, email or other internet-based services [39]. While telehealth has much to offer in the provision of remote care to patients, accessing it may prove a significant challenge to those most in need, including older people, those from socio-economically disadvantaged backgrounds, and those with physical or learning disabilities.

COVID-19 AND PREGNANCY

At present, limited information is available for pregnant women with COVID-19 in order to propose best practices for specialized care. However, the literature suggests that pregnant women with COVID-19 infection may develop severe clinical manifestations [40]. Therefore, surveillance systems for pregnant COVID-19 patients are being established to analyse the maternal and foetal outcomes. Also, awareness about management of COVID-19 positive pregnancies and prevention of neonatal infection is important for healthcare professionals. Proper vigilance and monitoring of the disease spread and rapid implementation of preventive measures are crucial to contain the spread of infection in the community. Readily available standard respiratory support to

manage severe COVID-19 infections in pregnancy is crucial and should be implemented rigorously by a multidisciplinary team. For better understanding, it is essential to help provide systematic data reporting for evidence-based clinical assessment, management and pregnancy outcomes in infected females that will guide healthcare facilities with limited resources to manage this vulnerable population in such an outbreak.

COVID-19 AND COMMUNITY HEALTH

Quarantine, hand hygiene, and face masks can potentially minimize the infection rate and mortality in the community [41]. The Qatari measures in Figure 2 need community participation, which is essential for a collective and socially acceptable response to preventing COVID-19. Engagement of local communities is essential to ensure compliance of lockdown until necessary measures are in place to ease the restrictions. In addition, there is a need for tailored national, regional, and community-based solutions for infection prevention taking into consideration the needs of our diverse population.

CONCLUDING REMARKS

There are direct effects of COVID-19 on individuals infected by the virus and their families and friends,

and there are indirect effects related to public health measures introduced to deal with the virus. The latter refers particularly to restrictions on movement of people due to quarantine and lockdown, which can affect individuals and the society in various ways. These will be key issues to address when Qatar moves to a recovery state post-COVID-19.

The rapid spread of COVID-19 is a sign of our globalised world. It is the new reality of public health, there will likely be variants or different corona-type viruses in the future. We have learnt several things already. First, at least 60% of the population has to get infected to achieve herd immunity, no country including Qatar has come near this proportion. Second, appropriate public health measures will only work with community involvement. Third, the health and well-being of migrant workers need to be considered as COVID-19 can easily spread in crowded work places and living quarters. Fourth, telemedicine can offer an opportunity for patients to consult health workers without being physically close. Fifth, we all need to be prepared for the population's mental health in the aftermath of COVID-19 and during its lockdown. Last, but not least, we need to be prepared for a second wave of COVID-19.

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