



Navigating COVID-19 in the developing world

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared a pandemic and a global public health emergency by the World Health Organization. This condition began in China in December 2019, was exported by international travellers and is now spreading by community transmission with cases reported in every country around the world. Over 3 million people are infected as of 2 May 2020, with over 240,000 reported deaths [1]. The case fatality rate is estimated at 1–5%, and no effective treatment has been clearly demonstrated for patients severely affected by the disease caused by SARS-CoV-2, named COVID-19.

Rheumatologists and clinicians world over are scrambling to advise and protect their patients from this infection. We know that patients with rheumatic and musculoskeletal diseases (RMDs), particularly those with systemic autoimmune diseases, are at increased risk of infections due to the RMD itself and due to immunosuppressive agents including corticosteroids and conventional synthetic, biologic, biosimilar and targeted synthetic disease modifying antirheumatic drugs (DMARDs). At present, however, there is no evidence that patients with RMD or patients on immunosuppressants fare worse in the COVID-19 pandemic than any other patient [2].

Current recommendations state that patients should continue their current RMD therapy, because a flare in disease activity may follow discontinuation of therapy. Such flares may result in an increased risk of infection, may require corticosteroid therapy and may need medical attention increasing the probability of being in contact with healthcare facilities and therefore with the virus [3, 4].

The antimalarial (AM) hydroxychloroquine (HCQ) and chloroquine (CQ) have demonstrated antiviral activity against severe SARS-CoV-2 in vitro and in small clinical studies [5, 6]. To date, however, no high-quality clinical data has shown clear benefit of AM, and a recent retrospective study failed to show that HCQ, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with COVID-19 [7]. Both HCQ and CQ are used by many RMD patients. Further studies will clarify the role of AM as prophylaxis or therapy in the COVID-19 pandemic, but our RMD patients should continue these therapies. In addition, tocilizumab is showing promise for the therapy of a severe COVID-19 cytokine release syndrome [8]. Additional information is needed in order to fully understand the utility of these interventions.

Low- and middle-income countries (LMICs) of the Southern hemisphere are bracing themselves for the SARS-CoV-2 pandemic and are potentially facing worse outcomes and different challenges than the hard-hit developed world [9]. This may be due to the significant burden of non-communicable diseases in LMIC, including cardiovascular illness, diabetes and lung disease, combined with the highest global prevalence of infections such as malaria, dengue, tuberculosis (TB) and HIV [10, 11]. Studies demonstrate that HIV-infected persons with low CD4 counts are at greater risk for influenza infection and its complications including pneumococcal co-infection, longer hospital stays and increased mortality, as well as prolonged viral shedding [12–14]. Persons with pulmonary TB (PTB) are at increased risk of influenza-associated mortality [15]. However, there is currently no evidence that HIV positive patients have poor outcomes

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in the SARS-CoV-2 pandemic, even in areas of high HIV prevalence such as Thailand [16]. In fact, antiretroviral therapy used by HIV positive patients may be protective from COVID-19 infection or serious complications, and there is interest in using HIV antiretroviral therapy to treat severe COVID-19, although very recently lopinavir–ritonavir has shown no benefit [17]. Endemic diseases in LMIC countries may not only increase the burden of SARS-CoV-2 in these populations but may also cause false positive screening tests, especially for dengue. This situation may delay the diagnosis of COVID-19 and therefore increase the spread of the virus, because in most dengue cases, there are no warning signals and the follow-up is ambulatory [18].

The brunt of most acute and chronic diseases is borne by the poor, and it is very likely that poor socio-economic status will impact on spread and outcomes of the SARS-CoV-2 epidemic. Overcrowded living conditions, food insecurity and poor access to basic amenities including water, congested public transport and shortage of personal protective equipment (PPE) for doctors, nurses and medical staff and SARS-CoV-2 infected patients all favour viral spread. Political disruption and poor education with lack of insight into the urgency of conforming to social distancing and lockdown measures may also hamper containment strategies. Care of patients with severe COVID-19 is challenging where healthcare capacities are already stretched thin, with a shortage of hospital beds (> 12 per 1000 population in much of Europe vs 1–2 in many LMIC), intensive care facilities (some European countries have 29 beds per 100,000 population, 35 in the USA and 5 or less in many LMIC countries), PPE and insufficient medical personnel (there are 2.7 physicians per 10,000 population in Africa and parts of South America compared with 21.5 in North Americas and 32.1 in Europe) [19–21].

Apart from its direct effects, the SARS-CoV-2 pandemic will bring chaos to fragile healthcare systems in LMIC. Currently, the day to day running of clinic services for chronic conditions including rheumatology outpatient clinics has stopped, jeopardizing new and existing patients' access to consultations, procedures and medication for months to come. Communications with our RMD patients is suboptimal with inadequate telemedicine platforms operational to date. In addition, both HCQ and CQ are now in short supply for patients taking it for RMD indications, as it has been snatched up for prophylaxis and therapy of COVID illness. Even once clinical services resume, the catch-up will be calamitous. We have seen how the recent Ebola epidemic greatly undermined malaria control efforts, resulting in an estimated 1 million malaria cases seen in West Africa in 2014 [22]. Similarly, the analysis of historic data shows that during the major influenza pandemics of 1889 and 1918, mortality due to TB significantly increased [23]. In Latin America, COVID-19 infection is an additional challenge for the health systems and economies

where recent Zika and Chikungunya outbreaks have had significant impact [24]. The economic consequences of the COVID-19 pandemic are likely to hit LMIC hard, pushing many patients and their families below the breadline and shrinking healthcare resources.

Thus far, Southern hemisphere countries where many LMIC lie are not as severely affected by the virus as their Northern high and upper middle-income counterparts. Because of limited testing, a consequence of resource constraints, the actual number of cases in LMIC is likely much higher than reported. However, even LMIC countries with more than 1000 confirmed infections have not yet reported the massive mortalities seen in the North. One may argue that the time between symptom onset and death ranges from 2 to 8 weeks and that Southern hemisphere countries are 4 to 8 weeks behind the Northern hemisphere [25].

The developing world may have some mitigating factors against the COVID-19 pandemic. The first is forewarning and a small window of preparation time. As the pandemic spreads, LMIC can study and learn from the successes and mistakes of the Northern hemisphere. Measures to contain transmission include discontinuing international travel, educating the public, restricting gatherings and timeously locking down all non-essential activities and planning clinical services for severe COVID-19 cases. Secondly, the virus seems to survive better in cold, dry weather with reduced ultraviolet light. The warm climate and the summer season in the Southern hemisphere may offer some protection. Age, a poor prognostic factor in COVID-19 disease, favours LMIC where less than 5 or 10% of the population is over 65 years, compared with 25–30% in Europe [26]. Genetic factors may also influence susceptibility, symptoms and outcome. The angiotensin-converting enzyme 2 (ACE2) gene encodes the cell-entry receptor of both SARS-CoV and SARS-CoV-2 [27, 28]. Polymorphisms in the ACE gene, associated with essential hypertension, are described in Africa and South America [29, 30]. Although very recent work has shown no evidence of ACE2 coronavirus binding-resistant mutants in different populations, further studies are needed [31]. Many LMIC countries remember well the lessons learned during SARS in 2003 and pandemic influenza in 2009. Protocols already developed during these crises, including laboratory and patient management, were designed and implemented in a scenario of limited resources. The protocols and previous experience with infectious diseases may be useful in this challenging situation [32].

Another potent advantage LMIC may have is resilience. Man versus nature is not a new battle here. Healthcare workers and patients have survived and often thrived through many challenges, including the ravages of infectious epidemics and the raw face of resource constraints. Rather than being misconstrued as “clinical deserts”, LMIC have clinicians with bedside expertise and experience in triaging and making difficult therapeutic decisions frequently without laboratory or

radiological investigations. In these COVID-19 times, clinical skills and experience working in very poorly resourced settings may be a major weapon in the armamentarium of healthcare providers. Images and video clips in the press from Italy and New York showing make-shift emergency rooms, beds on the floor and queues of desperately sick people waiting for care are familiar daily situations for many healthcare workers in LMIC.

The SARS-CoV-2 pandemic may be an opportunity to innovate. As seen in the SARS epidemic, this crisis can drive advances in undergraduate medical education [33]. With suspended classes, distant online teaching and learning including live-streamed webinars, video-based learning content, e-textbooks and group chats accompanied by online assessments to track student performance and monitor retention is taking place. For clinical students, as an alternative to real patient interactions, virtual patient platforms have been successfully used to teach and assess diagnostic skills [34]. To facilitate this, academic institutions must urgently focus on the availability of infrastructure, connectivity and equipment for learners and educators, frequently in short supply in LMIC. This should be seen as an investment, laying the foundation for more efficient medical teaching in the future.

We have incentive to improve telemedicine platforms, fortify patient support groups, strengthening collaborative work and continue research registries including the recently formed international COVID-19 Global Rheumatology Alliance (<https://rheum-COVID.org/>). This virus can bring us closer together and can highlight our similarities, strengths and connections. Unprecedented generous donations from private companies or individuals to assist small businesses and their employees affected by the coronavirus pandemic are a remarkable step towards reducing the gap between rich and poor in LMIC [35]. While LMIC focus on providing essential services while keeping frontline care providers safe, we look to surviving this pandemic and its aftermath with resilience and innovation.

Compliance with ethical standards

Disclosures None.

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