Invited Editorial

The response to COVID 19 across countries and the implications for future pandemics

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We have previously reported that COVID-19 was first identified in Wuhan, China, in December 2019[1-4]. By mid-August 2021, there were over 208 million confirmed cases worldwide with more than 4.3 million deaths giving a case fatality ratio of 2.1%[5]. Since COVID-19 is principally spread through airborne aerosols and physical contact[6-8], and an appreciable number of patients are asymptomatic, early strategies to prevent the spread of the virus in the absence of proven effective medicines included lockdown and other preventative measures (Figure 1) [4,9].

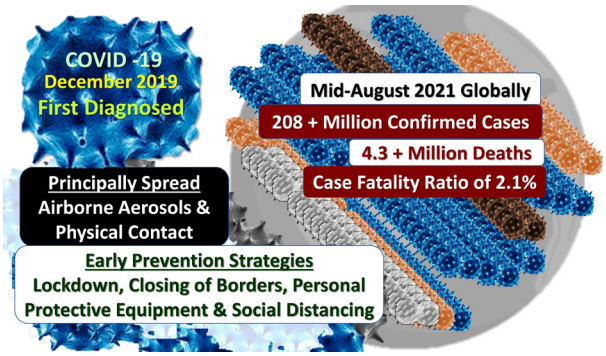

Figure 1: Current situation COVID-19 including prevention strategies

Published studies have shown increased screening, quarantining and social distancing to be effective and cost-effective in preventing and controlling the prevalence of COVID-19 over the long term[4,10-16]. However, there were appreciable differences in the rate at which lockdown and other measures were introduced across continents and countries, appreciably impacting on prevalence and mortality rates in practice[17,18]. Instigation of early lockdown measures among a number of Asian countries including Korea, Malaysia, Taiwan and Vietnam, as well as a number of African countries, helped prevent the spread of the virus in these countries certainly initially and limited the number of deaths[17-22]. There were though appreciable unintended consequences from early lockdown measures including both clinical and economic consequences[17,23-26]. Unintended consequences included appreciable reduced vaccinations for children especially in Africa with lack of public transport, clinic closures coupled with fears among mothers of attending clinics in case of contracting COVID-19, as well as rising rates of non-communicable diseases (NCDs) for similar reasons[17,24,27-29] (Figure 2). The rise in mental health disorders has also been a concern across countries[30-32].

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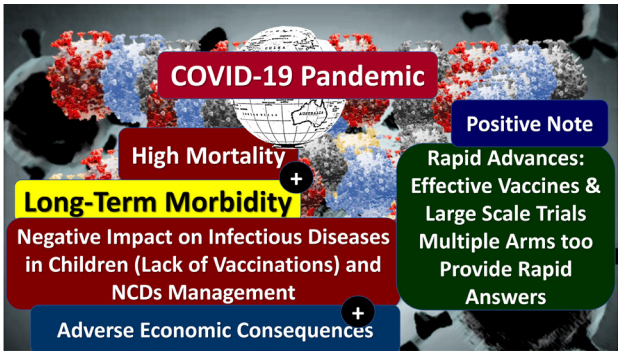

Figure 2: Clinical and economic impact of COVID-19

We have also seen an appreciable increase in the prescribing and dispensing of antimicrobials for patients with COVID-19 across sectors despite limited bacterial or fungal co-infections[22,33-37]. This is a concern as this will increase antimicrobial resistance (AMR) rates if left unchecked increasing morbidity, mortality and costs[4,38-40]. Several initiatives and strategies can be instigated to reduce inappropriate prescribing and dispensing of antibiotics across sectors for essentially viral infections[40-42], and we will be following these up. In hospitals, this typically involves the instigation of antimicrobial stewardship programmes (ASPs)[40,43-45]. Whilst it is recognised that ASPs are more difficult to introduce in hospitals among low- and middle-income countries (LMICs) due to resource and personnel issues, we are seeing a growing number of ASPs introduced across LMICs providing direction for the future[40,46-49]. Effective programmes in ambulatory care include educational initiatives among physicians as well as educational and other interventions among pharmacists[40,42,50-52]. We have seen limited dispensing of antimicrobials without a prescription in LMICs among patients with suspected COVID-19 where there are trained pharmacists available in pharmacies, with other national activities also helping reduce the self-purchasing of antibiotics[18-20,40,42,53]. Trained pharmacists can also help address some of the concerns arising from the COVID-19 pandemic including education especially around misinformation, helping with medicine supply especially among patients with chronic NCDs as well as increasing vaccination rates[17,54,55].

As mentioned in our previous publication, a key concern surrounding the pandemic has been the level of misinformation with potential treatments and the adverse consequences this has produced[4,56]. The imperative to try a range of re-purposed medicines at the start of the pandemic given rapidly rising case numbers resulted in a number of poorly controlled trials with unsatisfactory efficacy and safety data[57,58]. This was certainly the case with hydroxychloroquine where despite concerns with initial trial designs, early endorsement by governments, medical societies, and others resulted in appreciably increased use, shortages, rising prices and deaths in a number of LMICs[4,18.37,58-60]. However, later studies failed to show any meaningful benefit leading to recommendations not to use hydroxychloroquine for the treatment of patients with COVID-19 especially with the potential for increased cardiac events and hepatic failure[58,61,62]. Similarly other re-purposed medicines, including lopinavir/ritonavir and remdesivir, have failed to reduce morbidity and mortality in hospitalised patients following comprehensive clinical trials leading again to recommendations not to prescribe them[62-65]. In fact, to date, only dexamethasone has been shown in large well conducted clinical trials to benefit patients on respiratory support in hospital with COVID-19[66]. There is also increasing evidence to support the use of medicines such as tocilizumab[67-69].

However, despite the lack of effectiveness with a number of the re-purposed medicines, the large rapidly instigated studies by the WHO (Solidarity) and the UK (Recovery) with multiple arms including hydroxychloroquine, lopinavir/ritonavir, remdesivir and dexamethasone, have shown that it is possible to rapidly assess multiple medicines simultaneously in large cohorts to provide robust answers[61-63]. As a result, quickly provide treatment guidance and avoid the level of misinformation and its consequences that we have seen with medicines such as hydroxychloroquine with and without azithromycin[18,20,58,60]. This suggests it is possible to undertake robust trials simultaneously rather than in sequence when the situation arises providing direction for the future.

We have seen a number of other positive points arise from the urgency of the pandemic. These include capacity building to rapidly test patients as well as develop new low-cost tests where there are resource

concerns[17,21,70]. This could develop into new ways to streamline immunisation programmes where there are capacity issues both in terms of available vaccines but also support systems to administer them. Such mass monitoring could also potentially be used to rapidly track AMR rates across localities and countries through decoding the genomes of different bacteria given concerns with current surveillance methods among LMICs[71]. Such developments will enhance the potential for targeted interventional programmes to reduce high AMR rates among LMICs in the future. We have also seen a number of other innovations among LMICs to address concerns with identifying and managing patients with COVID-19. These include successful early sequencing of the COVID-19 genome in Ghana as well as the rapid development of different ventilators to address patients' needs among a number of African countries given shortages at the start of the pandemic[17,21], which also bodes well for the future.

Another positive outcome from the pandemic has been the rapid development of effective vaccines using different technologies including messenger RNA (mRNA)-based vaccines, with nanotechnologies here to stay[72-78]. This will be beneficial as more variants emerge in order to rapidly tweak vaccines[79]. Studies are now emerging of the differences in effectiveness, protection and adverse events between the different vaccines to guide future management strategies in different populations, with more studies ongoing[80]. We will be following this up in future research projects. However, again there have been concerns with the level of misinformation regarding the various vaccines including the level of side-effects, negatively impacting on uptake rates in practice[81-85]. Effective communication campaigns among all key stakeholder groups alongside potentially fining companies or groups for any misinformation, which is already happening among some African countries[17], are potential ways forward to address this.

Whilst children have a lower risk of COVID-19, as well as milder clinical manifestations when they are infected[86,87], they do experience a number of symptoms including fever, cough and diarrhoea[87]. Overall, approximately 6% of COVID-19 infected children appear to experience severe symptoms compared with an appreciable number of adults who have progressed to intensive care units to manage their condition in the absence of vaccines[88]. Since a large number of children with COVID-19 are asymptomatic[89], with most others experiencing milder symptoms if they do develop COVID-19, no deaths were reported among 416 cases of COVID-19 in children aged 1 to 9 years and a single death among 549 cases aged between 10 to 19 years in a recent study in China, and COVID-19 was very rarely fatal among children and young people in the UK even among those with underlying comorbidities[86,90], attention across countries towards children has typically focused more on the unintended consequences of COVID-19 including concerns whether routine vaccinations are being missed[27,40]. Alongside this, concerns with the appreciable prescribing of antibiotics in patients with COVID-19 including children[40], as well as concerns with orphanhood and caregiver deaths among children especially in LMICs and the implications for future psychosocial and economic support[91]. Economic hardship as a result of the pandemic is also increasing domestic violence against children especially in LMICs as well as increasing child marriages and child labour in LMICs such as Bangladesh, with concerns over child development during the coming years[92-94]. This needs to be monitored going forward.

However, the focus on children is changing with potentially increased morbidity and mortality with new variants. Potential treatments that have been researched in children include hydroxychloroquine, lopinavir/ritonavir, remdesivir, interferons, steroids and tocilizumab[95-99]. We will be shortly consolidating our findings, as well as reviewing current treatment patterns among a range of LMICs including Bangladesh, to provide future guidance.

In conclusion, the COVID-19 pandemic has resulted in multiple deaths and long-term morbidity across countries. However, there have been concerns with the unintended consequences of COVID-19 including the impact on NCDs incorporating mental health disorders as well as economic and other consequences including a rise in domestic violence. There have also been concerns with the level of misinformation regarding both prevention

and treatment, which needs addressing going forward including the instigation of evidence-based approaches among Governments, major Healthcare societies and patient organisations. On a positive note, we have seen rapid advances including the development of effective vaccines as well as the potential to conduct large scale trials with multiple arms simultaneously to provide rapid answers (Figure 2). We have also seen society adapt to a greater use of online platforms for the management of diseases including greater use of telemedicine and other approaches. This also includes greater use of online platforms for the teaching of pharmacy and medical students arising from early lockdown measures and closure of universities. There are though still issues of access and availability to internet bundles to address especially among LMICs to improve online teaching as well as undertaking clinical and practical teaching within a COVID-19 secure environment. This will also be the subject of future research projects.

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