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Commentary

Urgent needs to accelerate the race for COVID-19 therapeutics

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On December 8, 2020, a 91-year-old woman made history as the first person to receive the COVID-19 vaccine in the United Kingdom. Worldwide vaccination coverage will take time, especially in low-middle-income countries (LMICs) where access to coronavirus vaccines is limited and health systems are ill equipped to deal with sustained pressures associated with COVID-19. Meanwhile, hospital and critical care capacity will remain strained and basic therapies, including oxygen, are in urgent short supply.[1]

COVID-19 has disproportionately impacted the world's poorest and most vulnerable, posing additional challenges in achieving the Sustainable Development Goals.[2] In addition to basic supportive therapies, there are still not enough effective therapeutic interventions widely available. There remains an urgent need to develop efficacious COVID-19 therapeutics to prevent severity and mortality, and to forestall the collapse of overburdened health systems in resource-limited settings.

It has been over a year since the world's biomedical community began to contend this novel coronavirus. Having effective treatments to target COVID-19 stages would lead to significant benefits. These include treatments to (i) prevent the development of infections (ii) prevent disease progression, and (iii) reduce mortality. To better understand COVID-19 therapeutics, much had to be learned about the virus, disease evolution, how to conduct trials under pandemic conditions, and how to link testing and treatment strategies.

Two major therapeutic strategies based on disease pathophysiology were developed: antiviral agents, which aim to stop virus spread in the respiratory tract, and host-directed therapeutics (anti-inflammatory and immunomodulators), which have mostly become later-stage interventions aimed at preventing downstream consequences of severe COVID-19.

Initial efforts focused primarily on stemming the high mortality rates in critical patients and in drug repurposing. Several drugs demonstrated mechanistic plausibility and were initially tested for their *in vitro* activity on virus replication. Antiparasitic drugs, such as

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hydroxychloroquine and ivermectin, and antiviral drugs, such as lopinavir/ritonavir, were widely used while clinical trials were being conducted. Despite early hopes, results from multiple clinical studies did not meet expectations, hence not supporting use of these drugs[3] especially for severe cases. However, despite lack of evidence,[4] indiscriminate prescription with these drugs in many countries[5] has fueled misinformation and controversy.

According to WHO,[6] more than 2800 COVID-19 drug trials have been registered thus far. International platforms, such as RECOVERY, SOLIDARITY, PRINCIPLE, DISCOVERY, REMAP-CAP, TOGETHER, ANTICOV, are leading efforts to recruit large numbers of subjects while pharmaceutical companies are conducting their own trials. Global coordination, increased funding, comparable endpoints, open-source data repository and real-time information sharing will be key to meeting increasing demands for effective COVID-19 therapeutics.

Although much has been learned, questions remain about predictive factors for disease evolution and best approaches across the COVID-19 continuum, ranging from asymptomatic or mildly symptomatic patients to those hospitalized or who are critically ill, and to those living with long-term sequela of infection, as well as the impact of emerging variants on treatment efficacy. Therefore, widely available safe and effective antiviral therapies, administered early could help alleviate patient burden and potentially diminish the need for hospitalization.

To date only few drugs have been approved, registered, received Emergency Use Authorization (EUA) or qualified for WHO Emergency Use Listing. These include dexamethasone, remdesivir, bamlanivimab administered with etesevimab, casirivimab plus imdevimab, convalescent plasma, and the combination of baricitinib and remdesivir. Variable recommendations by different entities reflect the challenges to analyze, standardize and translate evidence into clinical guidelines including updates for immunomodulators such as tocilizumab and medications used for thromboprophylaxis. This reinforces the need to both harmonize and streamline clinical trials, while avoiding using the pandemic as an exception[7] to Good Clinical Practices.

Despite considerable policy and financing attention on vaccine development, the world still faces shortfalls in manufacturing capacity and supply for vaccines that have received emergency use authorization. This reinforces the need for greater global collaboration at early stages (pre-approval) so that overall capacity (especially biologics capacity) is optimally allocated to the most efficacious and field-adapted therapeutics (Table 1). It will also facilitate addressing proactively any upstream supply constraints. This is the mandate of the therapeutics pillar of ACT-A.[8]

Ending the pandemic is a matter of global health security requiring political leadership to ensure equal access to all tools once they are available. Promising treatment options, meeting the WHO Target Product Profiles (TPPs) for different patient categories, are advancing out of the pipeline, including immunomodulators as well as investigational new oral antiviral agents.[9] Thus, if approved, strong coordination and funding will be required to ensure quick uptake and rollout.

Universal access to COVID19 therapeutics can be approached across three main dimensions: availability, affordability and adoption. We can end the pandemic if patients are quickly diagnosed and

Table 1
Urgent Needs in LMICs and Access Dimensions for COVID-19 Therapeutics

Urgent Needs in LMICs		
• Sustainable oxygen supply for ill patients • Sustainable supply of effective therapeutics approved for COVID19 treatment • LMICs participation in trials, especially Africa-based trials • Boosting research of new tools to address rapidly spreading COVID19 variants • Fast uptake of diagnostic tests and supply of diagnostic tests • Inclusion of pregnant and lactating women and women of child-bearing age in clinical trials Outpatient and inpatient guidelines for COVID19 management • Support to national regulatory authorities • Robust investments to boost local and country level manufacturing capacity and supply chains		
Access Dimensions		
Availability	**Affordability**	**Adoption**
Robust investment in drug development, nourishing the pipeline with novel molecules and repurposed drugs	Ensure LMICs inclusion in licensing agreements and price negotiations between companies and ACT-Accelerator	Timely translation of trial results into treatment guidelines, with special focus on LMICs
Rapid assessment of drug candidates and timely data sharing	Coordination of transparent mechanisms to ensure equal distribution of treatments regardless of countries purchasing power	Strengthened and facilitate regulatory mechanisms to enable quick uptake in LMICs
Coordination and real-time information sharing on trial results to speed up progress	Anticipation of intellectual property barriers for scaling up production of generics fin LMICs	Global coordinated forecasting and pooled procurement mechanisms
Coordinated assessment of global manufacturing capacity and boosting investments to meet demands		Investments in robust international supply channels to enable equitable distribution, especially to LMICs
Strong global coordination on manufacturing capacity for therapeutics, in particular for monoclonal antibodies (mAb) where most of the manufacturing capacity is concentrated in few regions		Strengthening of surveillance and reporting mechanisms at country and global level to monitor safety issues after market entry
Global commitment towards capacity building plans, including technology transfer and funding in LMICs infrastructure to locally manufacture treatments at scale		
Robust collaboration between global policy makers and therapeutic developers/trial sponsors at early stage to ensure optimal capacity allocation to the most efficacious therapeutics, and any upstream supply constraints are proactively addressed		
Monitoring of ongoing agreements for scaling up access to quality assured therapeutics, especially to LMICs		

effective treatments are made widely available, affordable and readily adopted alongside the rollout of safe and effective vaccines (Table 1). Country adoption, community engagement, manufacturing capacity and global coordination will ensure no one is left behind[10] regardless of where they live.

Author contributions

CB, NS-W, SS and OE wrote the first draft of the manuscript. PH, MEB, and BL managed the process of review. All authors contributed equally and provided critical feedback, reference sources, and critical revisions for intellectual content and verified the information presented here.

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Declaration of competing Interest

MEB and PH are developers of a COVID-19 vaccine construct, which was licensed by Baylor College of Medicine to Biological E Ltd., a commercial vaccine manufacturer for scale up, production, testing and licensure. MG participates in one of eight SARS-CoV-2 vaccine development projects supported by The Scientific and Technological Research Council of Turkey (TÜBİTAK) since March 2020. SG is cofounder of Vaccitech and has a patent on ChAdOx1 nCoV-19 licensed to AstraZeneca. MH is Founder and Managing Director of SaudiVax. JPF and GK are members of the WHO SAGE Working Group on COVID-19 vaccines. GK is independent director of Hilleman Laboratories Private Limited and Vice Chair of the Board, Coalition of Epidemic Preparedness Innovations (CEPI). DK reports grants from Bill and Melinda Gates Foundation (BMGF) and grants from CEPI. JHK reports personal fees from SK biosciences. HL reports grants and honoraria from GlaxoSmithKline for training talks and from Merck as a member of the Merck Vaccine Confidence Advisory Board, outside the submitted work. TS reports grants from National Institute of Allergy and Infectious Disease and Fast Grants and research contracts from GlaxoSmithKline, and ViiV Healthcare. SS reports grants from Ansun BioPharma, Astellas Pharma, Cidara Therapeutics, F2G, Merck, T2 Biosystems, Shire Pharmaceuticals, Shionogi, and Gilead Sciences, outside the submitted work; and personal fees from Amplyx Pharmaceuticals, Acidophil, Janssen Pharmaceuticals, Reviral, Intermountain Healthcare, Karyopharm Therapeutics, Immunome, and Celltrion, outside the submitted work. All other authors declare no conflict of interests. The authors views and opinions in the Commentary do not necessarily represent the views, decisions, or policies of the institutions, universities, or health systems with which they are affiliated.

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