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Covid-19 Therapeutics Still Matter, Even with Vaccines

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Introduction

The world is a year into the Covid-19 pandemic. As cases continue to spiral out of control, driven in large measure by recent mutations originating in Brazil, Indonesia, South Africa and the UK, there is some cause for optimism. Vaccine candidates made by Pfizer/BioNTech, Moderna, and Oxford University/ AstraZeneca now have emergency use authorisation (EUA) in several countries. Meanwhile, Johnson & Johnson has applied for EUA in the US and Novavax should be reporting data soon, with the likelihood that their vaccine candidates will join the others made available for deployment. Even as most attention is given to Covid-19 vaccines, the role of treatment should not be underestimated. Vaccination programmes are moving slowly in rich countries, and low- and middle- income countries (LMICs) – especially those in Africa – are struggling to access enough vaccine doses for their populations, given both financial constraints as well as scarcity of supply. The latter is a result of a combination of insufficient manufacturing capacity and hoarding by rich countries. The research company Airfinity found that rich countries have purchased all of Moderna's vaccine and 85 per cent of Pfizer's, leaving the rest of the world to access vaccine candidates made by AstraZeneca, Russia (Sputnik V), and China (Sinopharm and Sinovac). [1] With China experiencing a Covid-19 outbreak and a public announcement of a vaccination programme that will reach 50 million people, it is unclear how it will balance domestic and external demand for its vaccines abroad. [2] The director-general of the World Health Organisation (WHO) issued an alarming statement that LMICs had vaccinated only 25 people while nearly 40 million people had been vaccinated in rich countries. [3] Credible estimates are that most poor countries will see only a small number of doses available this year to start covering vulnerable groups and health-care workers; for the bulk of the world's population, vaccine access may not become a reality until 2022 and 2023. [4] This is the current state of play as countries in Africa and elsewhere experience an alarming surge in new infections with health systems unable to cope. More terrifying is the spectre of Covid-19 vaccines being rendered less efficacious in the face of proliferating mutations, such as those from South Africa (B1351), the UK (B117) and Brazil (P1), among others. [5] These stark realities significantly raise the importance of quickly finding Covid-19 treatments, especially those that can be administered before hospitalisation is required. In summary, treatments are as important as vaccines and are, arguably, more important for LMICs in the short term until mass-vaccination programmes can be launched. For LMICs that are at the back of the line awaiting access to Covid-19 vaccines, a focus on treatment – especially antivirals – is a strategy that is immediately implementable with the right support.

A year into the pandemic, progress has been made in both repurposing drugs and developing new ones to treat Covid-19. However, such efforts are undermined by slow, fragmented, often underfunded clinical development and in some instances, manufacturing capacity. What is required is global coordination of clinical trials conducted at speed, more funding and increased manufacturing capacity, particularly for monoclonal antibodies.

Key Recommendations

1. **Additional funding must be immediately made for antivirals and diagnostic testing earmarked for LMICs.** The relevant global institution is Access to Covid-19 Tools Accelerator (ACT-A), with procurement via UNICEF and The Global Fund. The former supports drug procurement (dexamethasone) and the latter, Covid-19 diagnostics. As of November, the funding gap for the ACT-A was $4.2 billion for 2020, with an additional $23.9 billion required for 2021. [6]
2. **Financial support is needed for Africa-based clinical trials that are testing Covid-19 treatments.** They need to enrol more patients, test more drugs and expand to more countries.

- Support is critical for trialling drugs for hospitalised Covid-19 patients who do not require supplemental oxygen as many LMICs – especially in Africa –are short of medical oxygen and do not have the health systems to support mass hospitalisations.
- Support is critical for trialling drugs for those that test positive for Covid-19 but do not require hospitalisation. Several are highlighted in this paper.

3. **The time required for clinical development must be further shortened beyond the excellent innovations that are currently being used, such as adaptive design and shortening bureaucratic processes around reviews and approvals.** For example, artificial intelligence (AI) can be used for both research and development (R&D) as well as drug regulatory processes.
4. **The lack of manufacturing capacity that has plagued Covid-19 treatments such as monoclonal antibodies must be addressed so that each region has reliable production of these life-saving biologics.** This is important for both meeting current needs as well as being prepared for future pandemics.
5. **We reiterate our earlier call for global coordination of clinical trials**.

What is needed is centralised coordination of the full life cycle of Covid-19 treatment development activities. Such a coordinating function – which could be linked to the WHO's SOLIDARITY trial – should have two components. The first would aggregate and disseminate data collected from national drug regulatory bodies. In addition to creating a central repository of data on clinical trials, it would also help to shore up the drug supply chain. It would include data on:

- upcoming clinical trials with costs, data, and information on whether public or philanthropic money is supporting the trials
- approvals for emergency/limited use of investigational and unregistered interventions
- real-time reporting of drugs shortages and/or their active pharmaceutical ingredients (APIs) by both regulators and drug companies [7]

- other relevant data that may indicate potential problems, as an early warning system

The fact that many of these trials are supported by taxpayer money means that political leaders are better positioned to press for greater coordination. However, there are complex realities of how pharmaceutical companies and clinical development function. At the corporate level, the complexities of implementing such a platform (companies have different platforms and approaches to clinical research, legal issues, data ownership, and global representation) would have hampered the speed needed to start the trials. But given the presence of public funds that support clinical development, some additional political and institutional (regulatory agencies) coordination may be useful. This proposal presupposes capable national regulatory bodies, many of which do not meet WHO standards and need support. In such instances, alternative bodies that perform similar functions may be pressed into service, such as the African Vaccine Regulatory Forum. [8] This infrastructure should be maintained even as the pandemic wanes as it could be readily deployed when future pandemics arise. While national shortcomings in pandemic management have been laid bare by Covid-19, what is even more dangerous is the lack of global political leadership required to anchor the kind of global health security architecture that is critically needed given the obvious reality that pandemic anywhere is pandemic everywhere.

Drugs Are Needed, Now More Than Ever

The virus and its mutations will continue to spread in countries without mass-vaccination programmes. This means increased hospitalisations and deaths in absolute, if not relative, terms. Moreover, for countries with weak health systems this state of play portends both a humanitarian and an economic disaster – on this path, some governments will fall as desperation for relief from the pandemic grows unaccompanied by the tools available to richer countries. There are already widespread reports of overwhelmed public hospitals and insufficient supplies of medical oxygen, which is an urgent issue. Dexamethasone is one of the few drugs with full regulatory approval for treating Covid-19 that is cheap and widely available in Africa. Yet its effectiveness hinges on being administered to hospitalised patients who are on supplemental oxygen. The perverseness of having access to one effective drug but not to oxygen is not lost on health professionals in Africa and only underscores the glaring inequality between rich countries and LMICs. In addition, the data clearly show that mass illness has been a drag on the global economy, leading to the worst recession since the Great Depression as well as the spectre of double-dip recessions in the Eurozone and UK. [9] For countries in Africa that have the least access to Covid-19 vaccines, it also means being cut off from the international economy, isolated as a hotspot of disease. The continent cannot wait for vaccines. Nor can it wait for life-saving drugs that exist and need to be made immediately available.

The obvious point about treatments for Covid-19 is that they keep people from dying. An article published by leaders of the UK's RECOVERY trial and others found that using dexamethasone would mean that hundreds of thousands of lives could be saved globally. [10] Until there is full global vaccination, Covid-19 drugs and treatments will be desperately needed. What exists currently is insufficient to the scale of the challenge and need.

Of equal importance is the fact that scientific research strongly suggests that antivirals reduce the amount of viral load that is shed and by extension, disease transmissibility, especially if they are administered right after the onset of symptoms. [11] For example, advanced phase II/III clinical trials of an antiviral developed by Merck and Ridgeback Biotherapeutics are ongoing; in pre-clinical studies, data showed that transmissibility of SARS-CoV-2 was eliminated. [12] Of course, deploying this strategy depends on the availability of tests and the capacity to test at scale and then administer antivirals immediately.

Finally, vaccines have other shortcomings that increase the attractiveness and importance of antivirals: "The unlikelihood that a vaccine will be 100% effective, the incompleteness of vaccine coverage because of both vaccine hesitancy and the numerous logistical challenges to accomplishing prompt large-scale immunization of the majority of the population, the possibility of limited durability of vaccine protection,

the need for additional prophylaxis for high-risk subjects and poor vaccine responders, and the future value of effective antiviral treatment for Middle East respiratory syndrome (MERS) and new coronaviruses that will likely emerge from zoonoses." [13] In addition to these points, it is also not clear that existing vaccines can maintain their potency in the face of a proliferation of mutations. There is some evidence indicating that existing vaccines are less effective against certain strains, such as the one from South Africa. [14] The AstraZeneca vaccine offers "limited" protection against mild cases but stronger protection against severe disease, while Novavax and Johnson & Johnson vaccines were less effective at preventing disease in places where the South African strain is common. All of this increases the value of drugs that can work at the early stages of the disease.

The Big Picture

There is deserved admiration for the speed at which Covid-19 vaccines have moved through the clinical development process. What usually takes five, ten or more years was compressed into less than one. The US government-funded Operation Warp Speed is responsible for the clinical development of seven Covid-19 vaccine candidates, three of which have received emergency use authorisation, and one of which is likely to do so. [15] The US National Institutes of Health (NIH) is now putting together a programme to develop new antivirals, which are not likely to be ready in time to cope with the current pandemic. [16] Vaccine developers benefitted from more than $18 billion in funding. [17] Unfortunately, treatment development has not received the same level of support, with funding at just over $8 billion, with most money destined for the development of antibodies. These have been developed rapidly, which is critical given how potent they are as both a bridge to a vaccine as well as their efficacy in treating Covid-19. In addition to funding, scientists had extensive previous experience with antibodies, which allowed for faster development. Development of antivirals, which are critical to treating the disease (especially before a case becomes severe), has not received comparable levels of support and will become more important if vaccine-resistant strains emerge. Of the 12 treatments that are in clinical development through Operation Warp Speed, only three are not antibodies. [18] According to BARDA, Merck's MK-7110 MK-7110 "is unique in its ability to accelerate recovery while reducing disease progression in severe and critical hospitalised COVID-19 patients, with the potential to substantially reduce mortality," and is in phase III clinical development. [19] Genentech USA's MSTT1041A and UTTR1147A – which are in phase II clinical trials – are described by BARDA as "investigational medicines being developed for the potential treatment of hospitalized patients with severe COVID-19 pneumonia to prevent progression" to and recovery from ARDS. [20] Finally, Janssen is screening its library to find therapeutics with antiviral properties. It is noteworthy that all three therapies in clinical development are focused on hospitalised patients. More support is needed for treatments than can be administered outside hospital settings since the majority of Covid-19 patients do not require hospitalisation. The American programme is worth mentioning because the vaccines developed through that funding stream have been made available for purchase globally. The same will hold true for antivirals that emerge from US-supported clinical development.

Public funding in the UK for research on treatment takes place through National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI), which supports research into polyclonal antibodies with a grant of £400,000 [21] and monoclonal antibodies (mAbs) with £600,000. [22] These institutions also fund the UK's RECOVERY trial, which is the world's largest randomised control trial for Covid-19 therapies. There is a clinical trial dedicated to finding treatments that can be taken at home (PRINCIPLE), but it is smaller than RECOVERY.

With respect to repurposed drugs trialled for Covid-19, there are only a few that reached either EUA or approval and registration. All of these are for use in hospitalised patients. Most of the research supported by public money is not directed towards testing treatments for the disease before it becomes severe and requires hospitalisation and interventions such as supplemental oxygen and mechanical ventilation. Among initiatives supported by the US NIH, only four out of 12 are being trialled for non-hospitalised Covid-19 patients. [23]

Antivirals hold the most promise for treating those suffering from Covid-19, yet they have not received the support they merit. In some instances the cause is due to trials with low numbers of participants that yield inconclusive results, but there are a variety of other reasons. Often there are multiple trials testing the same drug, but they are not coordinated and have different trial endpoints, which undermines comparability; many trials also compete for patients. Second, the surges and lulls of the pandemic are such that recruiting patients can be challenging during a period of declining numbers of infections, which means too few people are enrolled in trials. Third, recruiting patients who are not hospitalised can be particularly challenging, as doing so requires strong coordination across relevant institutions. A person who tests positive for Covid-19 must be quickly identified and recruited for trial participation. Those conducting the trial need ready access to networks of hospitals and testing centres for this to happen seamlessly. Countries with centralised health services are better positioned to carry out such trials; the UK's NHS is part of what make the RECOVERY trial so valuable. In other instances, lack of funding is the binding constraint. Numerous research institutions and hospitals have identified promising therapeutics but lack the funding to move studies from pre-clinical to full development.

Effective treatments are desperately needed for all stages of the disease: drugs that will keep people out of hospitals; drugs that will shorten hospital stays; and drugs that will prevent hospitalised people from moving into critical care and intensive care. For LMICs that do not have the same health-care infrastructure as rich countries, the premium is on keeping people out of hospitals. Desperation partially explains why several governments have issued guidelines for medicines that either have not been subjected to rigorous double-blind, placebo-controlled trials or have not completed the trial process. Rich countries can better cope with hospitalised patients.

The Treatment Landscape

Drugs That Have Received Some Type of Authorisation

The therapeutics landscape has evolved significantly since the publication of our previous paper on therapeutics, as clinical trials have delivered clear evidence about which drugs work and which do not. The drugs currently available are all antivirals, which are believed to work best when administered early in the course of an infection, before the pathogen is able to inflict damage that leads to severe disease, the cytokine storm (where the immune system goes awry) and death.

At the time of writing, only a few drugs have received either full approval and registration or emergency use authorisation. Dexamethasone is approved for use in the UK, US and Japan. It is a steroid that decreases inflammation but does not directly inhibit viral replication; it has been clinically shown to reduce death among Covid-19 patients who are either on ventilators or receiving supplemental oxygen. Along with other corticosteroids, it is in widespread use, including in LMICs, where dexamethasone is the main treatment for Covid-19. Veklury (remdesivir) has received regulatory approval in Australia and Japan, and EUA in the United States, where it can be used for all hospitalised patients. It is administered intravenously, usually over five days. Gilead, which makes remdesivir, posits that the drug cannot be made in pill form because the chemical construction would affect the liver. Instead, the company is working on an inhaled form of the medication that would be delivered through a nebuliser, which turns liquid medicines into mist. [24] If successful, then it is possible that this oral form could be administered on an outpatient basis and be used in LMICs. The drug is currently in phase Ib/IIa trials, with a focus on participants with early-stage Covid-19. [25]

Some small studies indicate that Avigan (favipiravir) – originally used to treat influenza – might remove the virus from the airways. Despite the fact that its utility has yet to be shown in a large, randomised clinical trial, it has been approved to treat Covid-19 in China, Italy, Kenya, Russia, Saudi Arabia and Thailand. However, results from a recent trial in Kuwait show that Avigan does not work in patients with moderate to severe Covid-19; trials will continue in North America on those with mild symptoms. [26] Japan deferred approval on using Avigan in December. [27] Russia invested in rapidly trialling and eventually approving Avifavir (favipiravir) last June, while India and other countries trialled generic versions of the antiviral.

Added to this list just recently were tocilizumab (an anti-inflammatory treatment given by injection) and sarilumab. The UK government-funded REMAP-CAP clinical trial showed that the risk of death is reduced by 24 per cent when given to patients within 24 hours of entering intensive care. [28] Most of the

data comes from when the drugs were given in combination with a corticosteroid, such as dexamethasone. They will be made available for use immediately. There are other drugs that have emergency use authorisation in the US: convalescent plasma; Lilly's monoclonal antibody bamlanivimab (LY-CoV555); Regeneron's antibody treatment REG-CoV2; and the combination of the JAK inhibitor Olumiant (made by Lilly) and Veklury (remdesivir). The European Medicines Agency (EMA) recently commenced a real-time review of REG-CoV2 based on initial results from a study showing reduced amount of virus in non-hospitalised patients. [29] The EMA granted conditional marketing authorisation for Velkruy to treat adolescents and adults with Covid-19 with pneumonia who need supplemental oxygen. In September, the regulator gave authorisation for dexamethasone to be used for patients aged 12 and over who are hospitalised with Covid-19 and in need of respiratory assistance. Support for remdesivir is not universal, as the WHO has recommended against it and some studies suggest there is insufficient evidence that it reduces death.

Drugs Under Clinical Development

(See Table 1 for more information on drugs under clinical development) [30]

Antivirals

Drugs that are in use to treat other ailments have received attention for showing promise to treat Covid-19 in clinical development. For example, colchicine (an anti-inflammatory oral medication used to treat gout) may emerge as an effective oral treatment, particularly for treating non-hospitalised patients. The Montreal Heart Institute released data from its COLCORONA trial that show that colchicine could help higher-risk patients. The risk of developing severe Covid-19 and the number of hospitalisations was reduced when higher-risk patients were treated with colchicine, which helps prevent a cytokine storm and other complications. Overall, the drug reduced the risk of hospitalisation or death by 21 per cent. Data based on 4,159 patients diagnosed with Covid-19 showed that colchicine reduced mortality by 44 per cent, the need for mechanical ventilation by 50 per cent and hospitalisation by 25 per cent. [31] Results were submitted to a journal for peer review and the lead researchers of the trial expect that European, American and Canadian regulators will undertake a rapid review of the data. [32] The UK's RECOVERY trial is also trialling colchicine in patients hospitalised with Covid-19, and will randomly administer it to at least 2,500 patients. [33] This drug has particular relevance for LMICs as it is readily available at pharmacies, is inexpensive, and is easily administered outside of hospitals. The Montreal trial received funding from the COVID-19 Therapeutics Accelerator, an initiative launched by the Bill & Melinda Gates Foundation, Wellcome Trust and Mastercard. [34] This bodes well for its deployment in LMICs if it receives EUA.

Second, there is considerable enthusiasm for the insufficiently tested ivermectin, which is an inexpensive drug that can be purchased over the counter. It is used to treat both livestock and people infected with parasitic worms. It is worth mentioning that ivermectin has been used to treat onchocerciasis in Africa and several countries in Latin America for years, has existing distribution networks, and was donated by Merck in the billions of doses. [35] Early, non-peer-reviewed studies suggested that the drug may have antiviral properties, which has led to an explosion in its use to treat Covid-19, particularly in Latin America. [36] The use of the drug outside of clinical trials has made rigorous testing challenging. However, data have been released from a small trial that show promising results for the early treatment of Covid-19 that merit larger trialling of ivermectin: "This pilot, randomized, placebo-controlled, double blind trial failed to show a reduction in the proportion of PCR-positive patients seven days after ivermectin treatment; yet it shows a reduction in the self-reported anosmia/hyposmia and a (non-statistically significant) tendency to lower viral loads and lower IgG titers which presumably reflect milder disease," a paper presenting the findings said. [37] A meta-analysis of existing studies carried out by the US-based Front Line COVID-19 Critical Care Alliance (FLCCC) showed promising data that ivermectin reduces transmission, hastens viral clearance and decreases the death rate. [38]

Perhaps most striking is an analysis carried out on the use of ivermectin in Africa. The researchers "collected data from countries that routinely deploy prophylactic chemotherapy (PCT) using various drugs including ivermectin. [39] Based on the varying MDA designs, we grouped these countries into two different categories – those that include ivermectin in their PCT and those that do not. We then proceeded to compare Covid-19 proliferation between these two groups and further contrasted them against a third group of countries that do not use PCT at all." [40] The findings merit quoting at length:

" . . . countries with routine mass drug administration of prophylactic chemotherapy including ivermectin have a significantly lower incidence of Covid-19. Prophylactic use of ivermectin against parasitic infections is most common in Africa and we hence show that the reported correlation is highly significant both when compared among African nations as well as in a worldwide context. We surmise that this may be connected to ivermectin's ability to inhibit SARS-CoV-2 replication, which likely leads to lower infection rates. However, other pathways must exist to explain the persistence of such an inhibitory effect after serum levels of ivermectin have declined. It is suggested that ivermectin be evaluated for potential off-label prophylactic use in certain cases to help bridge the time until a safe and effective vaccine becomes available." [41] Ultimately, the drug needs rigorous testing.

Ivermectin is in widespread use in Argentina, Bangladesh, Bolivia, Bulgaria, Greece, Peru, the Indian state of Uttar Pradesh and several Brazilian states. The Republic of North Macedonia has issued guidelines for doctors on how to administer it. [42] The Slovakian health ministry recently approved ivermectin for use in hospitals as well as with a prescription. [43]

Third, Spanish pharmaceutical company PharmaMar makes Aplidin (plitidepsin), which is approved in Australia for the treatment of multiple myeloma, a type of blood cancer. In pre-clinical studies, the drug was shown to reduce viral replication of SARS-CoV-2 leading to a 99 per cent reduction of viral loads in animals' lungs. [44] The company is in advanced discussions with both British and Spanish regulators to launch phase III clinical trials. [45]

Other experimental antivirals have posted positive results in early clinical trials. For example, Ridgeback Biotherapeutics/Merck's molnupiravir recently advanced to phase IIa clinical trials. The drugs, originally developed for influenza, show some promise in treating both outpatient and recently hospitalised Covid-19 patients and are appealing because they are orally administered. Efficacy data may be less convincing due to trial design features. Experts "took issue with the recently hospitalised trial's primary endpoint of virological clearance, noting it lacks clinical value in the context of lingering side-effect concerns. This trial's recruitment of patients within seven days of treatment onset will also be challenging to execute due to logistical delays in practice … The outpatient trial would have been better-designed if it recruited patients according to their viral load and not symptom onset, as this would have allowed the trial to enrol patients with a consistent patient profile … However, others noted recruiting patients according to symptom onset is already challenging enough as it is, as outpatients feel they are not sick enough to participate in trials involving multiple onsite visits." [46]

Interferon beta (IFN-beta) is emerging as a promising antiviral. The naturally occurring protein has been shown to protect cells from infection against a number of respiratory viruses. The UK's University of Southampton and the company Synairgen are partnering on the development of SNG001, an inhaled interferon beta. What makes the drug unique is the oral inhalation approach. In December, the company announced that it was beginning phase III trials for the drug in the UK and 19 other countries, and that the US Food and Drug Administration (FDA) had granted the drug fast-track status and approved it for US studies. [47]

EXO-CD24, developed by Tel Aviv's Ichilov Medical Center, released data from phase I clinical trials showing that the new drug was successful in hastening the recovery of people with moderate to severe cases of Covid-19. Thirty patients were given EXO-CD24 and all recovered, 29 of them within three to five days. [48] It is administered by inhalation once a day. The basis of the drug is exosomes, which are carrier sacs that move materials between cells and deliver a protein, CD24, to the lungs, which are often damaged by Covid-19. [49] The drug will move into larger trials. Evidently, it can be produced quickly, efficiently and at low cost. Another experimental drug from Israeli researchers is worth highlighting: Allocetra, made by Enlivex. [50] The immunotherapy is used to treat serious Covid-19 cases by addressing the over-response of the immune system and inflammatory response that generate the cytokine storm that often results in death. The drug has completed phase II trials successfully. The majority of those in the trial had an additional risk factor for severe Covid-19 illness such as obesity, male gender and

hypertension. Sixteen severe and critical Covid-19 patients who received Allocetra survived a 28-day phase II clinical trial period. [51] Fourteen of the patients recovered, were discharged from the hospital by the end of the trial and were reported to be healthy. Two are still hospitalised in critical condition. The average hospital stay after receiving Allocetra was 5.3 days for those who were discharged. Based on the phase II trial results, Enlivex is submitting the data to regulators with the hope of securing an EUA for Allocetra to treat critically and severely ill Covid-19 patients. Phase III trials will enrol more than 100 people.

Finally, Roche paid Atea Pharmaceuticals $350 million for the ex-USA rights to the experimental antiviral AT-527, an oral, direct-acting antiviral that has been in phase II clinical trials on hospitalised patients with moderate Covid-19 and underlying conditions. [52] Importantly, the drug may work on non-hospitalised patients with some possible advantages over antibodies used outside hospitals: It is easier to manufacture at scale; it is cheaper; and it is oral, which makes it easier to administer. [53]

Antibodies

Antibody treatments will still be needed even once vaccines are in widespread use. (See **Table 2** for antibodies under clinical development.) They work in various ways: by targeting different parts of the coronavirus and by providing protection. They hold the potential to prevent Covid-19 infection if administered before the onset of symptoms, or before exposure to the virus, especially in high-risk populations. They also appear to be effective as a therapy for people who become sick. As such, they can serve as a bridge to a vaccine with a role to play after immunisation campaigns have been carried out.

There have been additional developments with antibodies since the publication of our last paper on therapeutics. Lilly, which received EUA for its LY-Co555 antibody from the US FDA in November 2020, posted additional trial results. Preliminary results from a phase III clinical trial showed it was ineffective in treating hospitalised Covid-19 patients. [54] More positive news arrived in January when results from a phase III trial conducted by the NIH's National Institute of Allergy and Infectious Diseases (NIAID) showed that LY-Co555 reduced the risk of developing symptomatic Covid-19 by 57 per cent among residents and staffers of long-term care facilities. [55] "BLAZE-2 is a first-of-its-kind Covid-19 trial designed to evaluate this vulnerable population by addressing the challenging aspects of running a clinical trial in long-term care facilities, which normally do not conduct them." [56] This innovation alone makes the trial noteworthy given the reality that many elderly people are unsuitable candidates for vaccines.

Second, AstraZeneca's AZD7442 is a combination of two long-acting antibodies (LAAB) derived from convalescent patients after SARS-CoV-2 infection. The company licensed it from Vanderbilt University Medical School, which made the discovery. More than 6,000 people are being enrolled in phase III clinical trials. The synthetic drug combination is designed to remain effective for between six and 12

months after a single dose is administered and it is expected to reduce the risk of resistance developed by the virus. [57] The longer period of effectiveness is because of AstraZeneca's half-life extension and reduced Fc receptor binding. The trial has two components: "PROVENT (NCT04625725) in the pre-exposure prophylaxis setting; and STORMCHASER (NCT04625972) in the postexposure prophylaxis setting." [58] Neither trial will be completed until 2022, which means that they are not available for deployment during the current surge in cases.

Third, the monoclonal antibody developed by GlaxoSmithKline/Vir Biotechnology is expected to behave in ways that are comparable to FDA-authorised Lilly and Regeneron in early Covid-19 disease. "VIR-7831 is a dual-action monoclonal antibody that was selected for clinical development based on its potential to both block viral entry into healthy cells and clear infected cells, as well as its potential to provide a high barrier to resistance." [59] GSK/Vir are currently carrying out "Phase II/III COMET-ICE clinical trial for non-hospitalised patients, the NIH-led Phase III ACTIV-3 in hospitalised patients, and a planned prophylaxis or prevention of symptomatic infection trial in 1Q21." [60] Interim data from COMET-ICE may be available imminently.

Fourth, South Korea's Celltrion Group announced in mid-January 2021 findings from its phase III clinical trial of CT-P59, its monoclonal antibody treatment candidate that could be used to prevent illness from Covid-19. The data show that CT-P59 is an effective treatment for patients with mild to moderate cases of Covid-19, especially for those aged 50 and over. Patients with mild-to-moderate Covid-19 experienced a 54 per cent reduction in the risk of developing severe Covid-19, while those with moderate Covid-19 experienced a 68 per cent decline. Recovery time also lessened and viral load decreased quickly and significantly through the seventh day of treatment. [61]

Our fifth example demonstrates how the pandemic has generated cooperation among competitors. Our first paper on therapeutics highlighted the leadership of Takeda in "conceiv[ing] and spearhead[ing] the CoVIg-19 Plasma Alliance, a collaboration that includes plasma companies with the support of global organisations outside the industry, [working on its] anti-Covid-19 Hyperimmune Globulin (CoVig-19) medicine." [62] Now Lilly, Vir and GSK are collaborating to evaluate "a combination of two Covid-19 therapies in low-risk patients with mild to moderate Covid-19. Lilly has expanded its ongoing BLAZE-4 trial to evaluate the administration of bamlanivimab (LY-CoV555) 700mg with VIR-7831 (also known as GSK4182136) 500mg, two neutralising antibodies that bind to different epitopes of the SARS-CoV-2 spike protein. This unique collaboration marks the first time that monoclonal antibodies from separate companies will be brought together to explore potential outcomes." [63]

Sixth, in late December 2020, Kiniksa Pharmaceuticals announced data from early-stage clinical trials of its mAb, mavrilimumab, in patients with severe Covid-19 pneumonia and hyperinflammation. Early results are promising. "Data showed an early signal of efficacy, with trends toward clinical improvement as well as lower mortality and shorter duration of mechanical ventilation in patients treated with

mavrilimumab on top of corticosteroids, including dexamethasone, and/or remdesivir." [64] The company is already enrolling patients in its phase II trial, which uses an adaptive design and is placebo-controlled, with data expected by the second quarter of this year. [65]

Seventh, Humanigen is partnering with the US Department of Defense's Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense to develop (and, assuming it makes it to EUA, to manufacture and distribute) lenzilumab, an mAb. The two have signed a Cooperative Research and Development Agreement (CRADA), which "ensures that federal experts work with the company on FDA meetings and regulatory filings, as well as provide comments on submission prior to submitting to FDA." [66]

Humanigen announced positive results in the late fall that its mAb showed positive effects on patient recovery, with about 37 per cent more recoveries in patients who took lenzilumab as compared with those were treated with the current standard of care. [67] The Phase III trial is exploring the effectiveness of lenzilumab in treating the cytokine storm that is responsible for so many Covid-19 deaths. The company hopes to apply to the FDA for EUA in the first quarter of this year.

Eighth, the Takeda-led CoVIg-19 Plasma Alliance has been in phase III trial since October. The polyclonal hyperimmune globulin (H-IG) is being developed to treat infected, high-risk individuals with Covid-19. Alliance members include Takeda, CSL Behring, Biotest, BPL, LFB, and Octapharma, BioPharma Plasma, GC Pharma and Sanquin, which all provide convalescent plasma. The collaborative approach is designed to hasten the therapy's development as well as offer it at scale. [68] Uber Health transports convalescent donors; Microsoft is contributing the Plasma Bot for donor recruitment as well as the Alliance's website; and the Bill & Melinda Gates Foundation offers advisory support. Phase III trial results are expected early this year, with discussions with regulators taking place thereafter. [69]

MAbs must be administered in infusion centres, which many health systems in LMICs lack. As a result, it is challenging to make them accessible. This may change as a result of a relatively new partnership. Merck KGaA, non-profit scientific research organisation IAVI, and India's Serum are working together to develop mAbs for Covid-19. [70] The group will develop the neutralising mAbs that IAVI and Scripps Research invented together. The research and development experience of IAVI and Scripps will be supported by the scaling and manufacturing experience of Merck and Serum. The latter is known as the manufacturing workhorse for medicines destined for LMICs. A main goal of the collaboration is to ensure equitable access to promising treatments for LMICs. The process will move at an accelerated pace from pre-clinical to clinical development with phase I trials expected early this year and plans for scaling up put in place if the treatments are shown to be effective in early testing. [71] While Merck will be responsible for commercialisation in rich countries, Serum will lead on commercialisation in LMICs as well as global manufacturing. [72]

Finally, one other initiative in the mAb space is worth highlighting as it has the potential to be administered at scale and with ease in LMICs if it makes it through clinical development, because it is inhalable. Aridis Pharmaceuticals has identified AR-701 by using its proprietary APEXTM platform technology to screen [convalescent plasma] from American and European patients. [73] "AR-701 is comprised of multiple fully human IgG1s monoclonal antibodies directed at conserved regions of the SARs-CoV-2 envelope proteins. AR-701 mAbs are designed to maintain broad coverage of SARs-CoV-2, including recently reported variants of SARS-CoV-2 such as the D614G variant and possible future variants. Furthermore, AR-701 mAbs have been engineered to prolong the duration of protection well beyond that afforded by typical mAbs. AR-701 is designed to block the binding and propagation of infection by SARS-CoV-2 of human lung cells." [74] The ultimate goal is for AR-701 to be self-administered for people with Covid-19, whether or not they have symptoms. Doctors can send the prescription to a pharmacy for the patient to collect the aerosol spray and administer it themselves immediately. An effective treatment such as this is needed for non-hospitalised people with mild-to-moderate symptoms and asymptomatic cases, who are vectors for the disease's spread, [75] and it could be game-changing since the majority of Covid-19 cases are in people who do not require hospitalisation. [76] The low-dose aerosol therapy would be taken just once and could possibly be in a dosage that is 100 to 1,000 times lower than that of either IV or intramuscular administration because it is inhaled into the lungs. [77] Phase I/II clinical trials are launching this quarter, with phase III enrolment likely to be complete by the end of the year.

Other drugs that showed promise in early clinical development have not fared as well. Our previous paper highlighted AstraZeneca's entrant, Calquence, which made it to phase II trials with encouraging results before being shown ineffective. [78] In late January, the UK's PRINCIPLE trial provided conclusive evidence that neither doxycycline nor azithromycin – both antibiotics – are effective treatments for Covid-19. [79] A few studies have provided clear evidence that hydroxychloroquine does not work, yet it remains the standard of care in many African countries.

Some LMICs are carrying out trials that focus on pre-hospital and non-hospital cases. In the context of fast-spreading mutations, the need for drugs to keep people out of hospitals is growing exponentially, even in rich countries. LMICs have been much faster to move drugs through the clinical development process, or even allow their use without full clinical development since they often lack the resources to carry out rigorous randomised, double-blind, placebo-controlled trials.

Streamlining Clinical Trials

The Covid-19 pandemic has shown the importance of bringing therapeutics to market quickly but safely. Progress has been made in shortening the length of clinical development. Two types of changes are worth highlighting. First, significant amounts of time in clinical development can be reduced by addressing administrative and bureaucratic hurdles. For example, the UK's RECOVERY trial is often cited as a model that streamlined the process.

- "It had a short, flexible protocol – just 20 pages long – that laid out the design and data and regulatory requirements, and allowed trial arms to be halted or added.
- It received ethical and regulatory approval in just 9 days, compared with the standard 30–60 days.
- Its recruitment procedures were straightforward, with only a two-page consent form and a one-page bedside form to be completed by clinicians.
- It accelerated data collection and processing through NHS DigiTrials.
- And it quickly made results public — the announcement was followed by a preprint on the medRxiv serverand journal publication within a month." [80]

The other innovation is the move away from traditional trials to the use of adaptive clinical trials. A traditional phase III trial "must recruit patients to its own control group and test just one hypothesis … whereas an adaptive trial platform allows [researchers] to simultaneously test multiple interventions against a single, shared control arm, add and eliminate treatments as the trial progresses, and update the study design as the treatment landscape changes." [81]

Additional efficiencies can be gained through applying AI to research and development (R&D) and drug regulator processes. Drug companies have yet to take full advantage of the treasure trove of data generated by its capture in the R&D process to guide and inform decision-making. The Covid-19 pandemic demands that actors involved in clinical trials glean insights from these data "eg, data from real-world evidence (RWE)/ real-world data (RWD), secondary research data, data from patient interactions like patient services, data from public sources about regulatory submissions/ pathways). This will have far reaching implications for companies in areas including early approvals for new drugs, identifying right disease characteristics to streamline research and clinical trials, using NLP for actionable insights from patient perception and usage of drugs, developing a smart regulatory intelligence platform and developing an optimal submission pathway for drug approvals across various regulatory guidelines in different countries." [82]

UK Clinical Trials

Within the UK, there are three significant clinical trials for Covid-19 treatments: REMAP-CAP, RECOVERY and PRINCIPLE. REMAP-CAP is designed "to determine and continuously update the optimal set of treatments for community-acquired pneumonia." It has been adapted to respond to the Covid-19 pandemic, and will test the following:

- "Antiviral therapy: evaluating no antiviral therapy for Covid-19 (and no placebo), lopinavir/ritonavir (Kaletra), hydroxychloroquine, and the combination of hydroxychloroquine and lopinavir/ritonavir
- Immune Modulation therapy: evaluating no immune-modulating therapy for Covid-19 (and no placebo), Interferon-beta-1a, interleukin-1 receptor antagonist (Anakinra), tocilizumab and sarilumab.
- Antibody therapy: evaluating the use of convalescent plasma for Covid-19
- Therapeutic anticoagulation: evaluating the use of low molecular-weight heparin or unfractionated heparin compared to standard pharmacologic thromboprophylaxis
- Vitamin C: evaluating the use of high-dose vitamin C for patients with severe CAP including CAP caused by Covid-19" [83]

RECOVERY Trial

The UK's innovative platform for trialling Covid-19 drugs is responsible for delivering clear evidence about the effectiveness of dexamethasone. There are several drugs that are currently being trialled:

- Low-dose dexamethasone (now only recruiting children)
- Colchicine (commonly used anti-inflammatory)
- Tocilizumab (an anti-inflammatory treatment given by injection)
- Convalescent plasma (collected from donors who have recovered from Covid-19 and contains antibodies against the SARS-CoV-2 virus)
- Regeneron's antibody cocktail (a combination of monoclonal antibodies directed against coronavirus)
- Aspirin (commonly used to thin the blood) [84]

Note that there is overlap in the drugs being trialled in REMAP-CAP and RECOVERY: tocilizumab and convalescent plasma.

What we know less about is what applications they have received, how they plan to triage them and over what time period they will scale. It would be invaluable to understand how the most urgent treatments

can become available before the full rollout of vaccines and antibody treatments. Also unclear is the full extent of the RECOVERY team's capability and what resources would help them move faster.

Second, in addition to rapid triaging and agreement on trials, more government support should be dedicated to small-scale but promising work. It would be akin to the research and development category that the Labour government under Tony Blair used to allocate additional university research funding as it enabled small and less prominent pieces of research to see the light of day. It was never a large amount and it tended to go to the best teams (so it was not throwing money towards a "punt"), but remarkable results came through this channel including, for example, some of the small-scale but extraordinary work at the Diamond Light Source (Harwell Science and Innovation Campus), the UK's national synchrotron that works like a giant microscope. By using the power of electrons to produce bright light, scientists can better study things like vaccines and viruses, fossils, and jet engines. [85] Putting in place this kind of nimble research architecture is of critical importance not just for this pandemic, but any pandemics that occur in the future, and would provide more supply for early phase trials.

PRINCIPLE

PRINCIPLE is a nationwide clinical study from the University of Oxford to find Covid-19 treatments for the over 50s that can be taken at home. Within that demographic, the focus is on people with underlying health conditions. The trial is also open to people over 65 with symptoms; they can participate even if they do not have any underlying health conditions. "Delivered through primary care, PRINCIPLE is evaluating whether treatment early on in the community can help people aged over 50 recover quickly from Covid-19 illness, without the need for hospitalisation. PRINCIPLE is currently evaluating azithromycin and doxycycline, which are two commonly prescribed antibiotics. These drugs are thought to have antiviral and anti-inflammatory properties against coronavirus, and also treat bacterial infections like pneumonia, which is a common reason for deterioration in people with Covid-19, and excessive inflammation is a cause of complications." [86] This trial may turn out to be quite consequential in terms of relevance for LMICs that have weak and stressed health systems, given that the drugs can be administered at home.

Global and Regional Clinical Trials

SOLIDARITY [87]

The international clinical trial, launched by the WHO, is designed to find treatments for Covid-19, focusing on three outcomes: length of hospital stay, mortality and the need for assisted ventilation. It is being run in more than 30 countries and has enrolled almost 12,000 patients in 500 hospitals. It is one

of the largest international randomised trials. After several months of study, the steering committee released interim results in mid-October 2020:

"It found that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients . . . This decision applies only to the conduct of the Solidarity Trial in hospitalized patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for Covid-19." [88] It is unclear what the next round of drugs to be trialled will include.

ANTICOV in Africa

African leaders and scientists early on called for more clinical trials for treatments and vaccines to take place in Africa. Local trials matter for several reasons. First, African countries are routinely underrepresented in clinical trials. Second, weak infrastructure, lack of visibility of existing sites, and inconsistent clinical trial regulatory timelines all hamper investments but do not excuse the danger in excluding the continent from clinical trials. [89] Third, the continent is home to significant genetic diversity, which is necessary for generalising clinical trial findings to the general population. [90] There is evidence from other drug and vaccine development efforts that lack of diversity during clinical trials can have dire consequences. As pointed out during the efforts to find HIV antivirals, commentators observed that in the case of the anti-HIV drug efavirenz, "It is metabolized more slowly among people of African descent. Since the numbers of African Americans in the study were too few to be able to discover this, the metabolism difference led to resistance issues for many people taking the drug. Had more data been collected at the outset, it is possible that this particular complication could have been avoided for many people." [91] Attention to vulnerable and excluded populations must be built into clinical development for drugs to be successfully deployed to LMICs.

While there are hundreds of trials for possible Covid-19 drugs taking place globally, there are very few in Africa, but there is some progress. An example is the collaborative effort launched by an international network of research institutions and 13 African countries, focusing on mild-to-moderate Covid-19 outpatients. The ANTICOV consortium is coordinated by the Drugs for Neglected Diseases initiative (DNDi), an international non-profit drug research and development (R&D) organisation that has extensive partnerships in Africa. Twenty-six major international and African R&D organisations are participating. Thirteen countries and 19 sites are included. The aim is to find cheap, readily available drugs that can keep those suffering from Covid-19 out of hospital, so that already-weak health systems are not overwhelmed. More specifically, the trial seeks to find a drug that reduces by half the likelihood that mild Covid-19 cases progress to severe illness. [92]

According to a press release from DNDi, "ANTICOV is an open-label, randomised, comparative, 'adaptive platform trial' that is testing the safety and efficacy of treatments in 2,000 to 3,000 mild-to-moderate Covid-19 patients in Burkina Faso, Cameroon, Côte d'Ivoire, the Democratic Republic of Congo (DRC), Equatorial Guinea, Ethiopia, Ghana, Guinea, Kenya, Mali, Mozambique, Sudan, and Uganda." The trial's objective is to find treatments that can both limit the development of severe Covid-19 and decrease transmission. [93] The platform trial is adaptive and takes clinical trials used for cancer drugs as its model. The structure allows the simultaneous testing of several treatments. Moreover, fast decisions can be made quickly, including using real-time analysis of results to add, continue or halt treatments arms.

Most Covid-19 cases in Africa are either asymptomatic or mild; hence the ANTICOV trial focuses on trialling dugs that could effectively treat mild to moderate cases. The researchers running the trial are working with ACT-A to choose the most promising treatments, based on global scientific research. Unitaid and the UK-based Wellcome Trust are the convenors on behalf of ACT-A. [94] The first drugs to be tested include lopinavir/ritonavir, which is the HIV anti-retroviral combination, and hydroxychloroquine. Despite the fact that studies such as the WHO's SOLIDARITY trial have concluded that the drug is not effective against Covid-19, hydroxychloroquine remains the standard of care in many African countries and features in the ANTICOV trial. Other possible drugs under consideration for the trial include those that are used to treat some cancers, hepatitis C, malaria and parasitic infections. [95] The approach is clearly to identify drugs that are locally available and easy to administer, particularly outside a hospital setting.

Covid-19 Therapeutics in LMICs: Focus on Africa

Critical Care Capacity in Africa Is Low, Making Therapeutics More Important

Our earlier report, *How the Therapeutics Landscape is Evolving*, affirmed the argument that "effective treatments will prevent health-care systems from being overloaded, keep people off ventilators, shorten hospital stays, and allow those who are infected to remain healthy and able to live their lives, including returning to work." [96] The reality is that health systems in LMICs are not as robust as those in rich countries. With respect to Africa in particular, the picture is dire. Critical-care capacity is low, with evidence emerging that it is being stretched to the breaking point by Covid-19.

One study found the following:

"Across the continent, there were an average of 135.19 hospital beds and 35.36 physicians per 100,000 people ranging from 67.39 beds and 9.57 physicians per 100,000 people in low-income countries to 302.50 beds and 115.24 physicians in upper middle-income countries. The average number of hospital beds per 100,000 was highest in Southern Africa and lowest in West Africa, while the average number of physicians per 100,000 was highest in North Africa and lowest in West and Middle Africa.

Across all 54 countries included in the analysis, there was an average of 3.10 ICU beds and 0.97 ventilators per 100,000 people. The average number of ICU beds per 100,000 people ranged from 0.53 in low-income countries to 8.59 in upper-middle countries and 33.07 in Seychelles, the sole high-income country included in this analysis. The average number of ventilators per 100,000 people ranged from 0.14 in low-income countries to 2.49 in upper-middle income countries. The average number of ICU beds was lowest in West Africa with only 1.10 ICU bed per 100,000 people, and the average number of ventilators was lowest in East Africa with only 0.23 ventilators per 100,000 people.

Overall, there was an average of 2.42 total (physician and non-physician) anaesthesia providers per 100,000 people ranging from 1.24 and 0.66 in low-income countries and in the Middle African region, respectively, to 6.91 and 6.64 providers per 100,000 in upper middle-income countries and the North Africa region, respectively." [97]

For several months into the pandemic, it appeared that LMICs might be spared the harshness of the disease. Africa in particular posed a puzzle to epidemiologists, who tried to understand the relatively low infection, hospitalisation and death rates. For example, as of early September, Africa had "more than 1.2 million symptomatic cases and 30,000 deaths, with a 2-4 per cent case fatality" and 5 per cent of the

world's infections at that point). [98] Explanations for the comparatively better outcomes ranged from a young population and a favourable climate, to quick action by governments and community adherence to guidelines. [99] Cautious optimism that perhaps the worst had past has given way to sobering assessments, especially in light of the fast-spreading mutation that originated in South Africa. The fall/winter surge in Covid-19 cases has hit the continent – and other LMICs – particularly hard. South Africa stands out as among the worst affected, with the WHO's Africa region reporting that the country registered more than 70 per cent of new weekly cases (excluding Djibouti, Egypt, Libya, Morocco, Somalia, Sudan and Tunisia) on the continent. [100] The rest of the Africa region is seeing sharp increases as well, and in the four-week period ending 3 January registered the world's biggest increases in cases; moreover, there was a 28 per cent rise in deaths the previous week. [101] Finally, Africa's Centres for Disease Control reported that about 39 out of 55 countries had seen a surge in cases. [102]

These data have clear and alarming ramifications for the continent's health systems. These figures also matter for what the continent and other LMICs in a similar position need in terms of drugs to treat patients. Africa imports more than 80 per cent of its medicines, which in the context of the growing burden of Covid-19 cases, is unsustainable.

Global Access to Covid-19 Tools (ACT-A)

African governments in need of Covid-19 drugs can purchase from drug companies directly. The global Access to Covid-19 Tools Accelerator (ACT-A) initiative is trying to facilitate critical products for LMICs, including Africa. It was launched in April 2020 by WHO and participating global health organisations: the Coalition for Epidemic Preparedness Innovations (CEPI); Gavi, the Vaccine Alliance; the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund); Unitaid; the Foundation for Innovative New Diagnostics (FIND); the Wellcome Trust; the World Bank Group; and the Bill & Melinda Gates Foundation. ACT-A is a framework for collaboration, not a decision-making body or a new organisation. It was set up in response to a call from G20 Leaders in March 2020 and comprises four pillars: Diagnostics, Therapeutics, Vaccines (also known as COVAX), and the Health Systems Connector pillar which works across the other three. Each pillar is managed by two or three partner agencies. [103] Wellcome Trust and Unitaid are the co-leads for therapeutics. Additionally, the WHO leads on the cross-cutting Access and Allocation workstream. High-income countries are not permitted to participate.

"The Covid-19 Therapeutics Accelerator is distinct from other similar efforts including:

- Focused on securing prompt and affordable access of products in LMICs
- End to end focus, including manufacturing and scale-up

- Agile and flexible funding processes, including at-risk to accelerate
- Payout has no geographic restrictions
- Focused on pre- and post- exposure prophylaxis for high-risk individuals as well as mild/moderate disease treatment" [104]

The immediate need that the therapeutics pillar is addressing is finding drugs for LMICs, with a focus on marginalised communities. "It is analysing over 1,700 clinical trials for promising treatments and has secured dexamethasone for up to 2.9 million patients in low-income countries. The Global Fund and UNICEF are the institutions that are actually procuring dexamethasone for LMICs. Access to dexamethasone has been expedited through an emergency use listing (EUL) procedure, publication of treatment guidelines, and the creation of a stockpile for emergency use." [105] It has also secured an agreement to help facilitate future access to monoclonal antibody therapies in low- and middle-income countries.

The main constraint – as far as can be determined from publicly available documents – is funding. The total committed is just over $6 billion – but an additional $3.5 billion is needed urgently. For 2021, the funding gap is $23.7 billion if tools are to be deployed across the world as they become available. These numbers are not disaggregated, so do not take specific account of the funding gap for treatments alone. However, public statements on promising therapies made by Dr Nick Cammack, head of the Wellcome Trust's Covid-19 Therapeutic Accelerator project, are suggestive. In statements made on 7 October 2020, he argued that there needs to be more "global funding and the engagement of large and small companies" in this space, highlighting that £1.5 billion has been pumped into the race for a vaccine, while only £232 million has been invested in the research and development of treatments. [106] What is unclear from the statement is what institutions are bound up in the term "global funding." Moreover, updated figures on the funding gap are not easy to find but will be available when the strategy and total commitments are refreshed in the coming days. At the very least, we know that the gap between funding for vaccines and for treatments is stark. Dr Cammack also made the following statement about total funding needed: "We've estimated that to provide treatments around the world, it will probably need $7 billion (£5.4 billion) – a huge number, I know, but compared with a probable $7 trillion (£5.4 trillion) economic hit, it's minuscule." [107]

While dexamethasone is cheap and is readily available, it is administered to Covid-19 patients who are using supplemental oxygen. News reports have indicated that many hospitals on the continent are running out of oxygen, with both hospitals and their suppliers caught off guard and scrambling to provide it quickly. The shortage extends elsewhere in the supply chain to oxygen tanks, as some patients may use up to ten per day; and drivers need to be trained to drive oxygen tankers. [108] Interviews with informed sources suggest that demand for the drug is just beginning to increase, probably because the surge in cases requiring hospitalisation is just now becoming evident.

It is unclear whether the ACT-A will provide assistance in sourcing other drugs, such as remdesivir. Last summer, Cipla South Africa was given a license to manufacture and distribute remdesivir, after signing an agreement with Gilead Science to distribute the antiviral to 127 countries, including South Africa as well as well as several other countries in sub-Saharan Africa. [109] The company has made a commitment to pricing remdesivir lower than or similar to prices in other developing countries in order to ensure greater access. [110]

The ACT-A mentions a commitment to making antibodies available for LMICs. The main companies furthest along in clinical development are Lilly and Regeneron, both of which have received EUA in the US and elsewhere, though not in the UK (phase III clinical trials are ongoing). Lilly is part of the Therapeutics Accelerator programme and has a particular approach that it is using to guide decision-making: "To guide decisions on where to send the medicine, [Lilly is] taking a data-driven approach. Priority countries and quantities of medicine will be determined using data from trusted research centres such as the John Hopkins University Coronavirus Resource Center and international health authorities such as the World Health Organization. Because the pandemic is moving fast, [Lilly will] commit only to a few months of supply at a time to any given country so that [Lilly] may best match demand and limited supply." [111] There are no programmes underway in sub-Saharan Africa as of yet, nor have any governments granted EUA for LY-CoV555, except for Morocco.

With respect to manufacturing, Lilly's partner to scale up production specifically for LMICs is Fujifilm, which will double production at its site in Denmark, bringing it to a total of 12 20,000-liter bioreactors by fall 2023, making the Denmark facility one of the few major large-scale manufacturing facilities in the bio-CDMO industry. The development will also include the addition of the Denmark site's first fill/finish production line (added by summer 2023), featuring a fully automated, cutting-edge system capable of producing up to approximately 35 million units per year to cater to large-scale production. In spring 2022, a new packaging line equipped with facilities to assemble multiple types of auto-injectors as well as automatic labelling, will be added. The advanced capabilities at the Denmark site led to the announcement of future manufacturing capacity reservation by the COVID-19 Therapeutics Accelerator. The facility holds six 20,000-liter bioreactors and will double in capacity as part of a $928 million expansion project announced in June. [112] In terms of when LY-CoV555 will be available, commercial manufacturing should begin in April.

Regeneron and Roche – which is responsible for manufacturing REG-CoV2 outside the US – share a commitment to making the antibody cocktail available to Covid-19 patients around the globe if approved and will support access in LMICs through drug donations to be made in partnership with public health organisations. The company is working with the WHO ACT-A to explore access through donation and will continue working with them and other groups regarding access to casirivimab and imdevimab in LMICs. The company will be able to supply over 2 million in 2021.

For antibodies to be widely accessible in LMICs, several changes will be necessary that require global cooperation. Not many antibody-based treatments are licensed in LMICs; there are not established, efficient policy and regulatory pathways to make them available, even if they were affordable. [113]

IAVI and Wellcome have outlined several steps to make mAbs accessible to LMICs. Beyond a campaign to raise awareness of the benefits and economic value of mAbs, the two global health organisations call for three steps that are worth quoting at length:

- "mAb product developers, policy makers, and health care providers must partner early in development to help ensure that future mAb products are acceptable and feasible to implement in LMICs. Policy makers and regulators must harmonize and expand the scope and utility of policies and collaborative regulatory pathways, currently in use for vaccines and small molecule drugs, to enable broader registrations of mAbs in LMICs. For example, regulators could support, and product developers could use, collaborative regulatory initiatives between stringent regulatory authorities—such as the European Medicines Agency and the Food and Drug Administration—and other national regulatory authorities to address limited regulatory capacity in LMICs.

- Product developers and funders must invest in and apply new technologies to lower development costs. Advances in identifying, engineering, manufacturing, packaging, and delivering more potent monoclonal antibodies could help to lower production and delivery costs and thus reduce their price. A few recent examples demonstrate that antibody prices don't have to be in the thousands of dollars per dose—some manufacturers in India are marketing lower priced ($20–$40 per dose) innovative antibodies for post-exposure prophylaxis of rabies, and lower-price biosimilars for cancers (less than $200 per dose) are starting to emerge in some parts of the world.

- Product developers and public entities must establish and use alternative business, pricing, and procurement models to enable innovative and broader market approaches in low-, middle-, and high-income countries. For example, some multinational companies are starting to market second brands, at significantly lower prices, in LMICs to broaden access beyond high-income countries. A few pharmaceutical companies are starting to adopt more comprehensive patient access approaches by strengthening health systems and improving capabilities to diagnose and treat disease in LMICs to define the market size and demand forecast for mAb products." [114]

There is some evidence that the South African mutation may be resistant to certain antibodies, thereby undermining their effectiveness. More testing will be necessary but there is some indication that combining mAbs into polyclonal cocktails could work against the mutation. For example, Regeneron, Columbia University and NIH researchers confirmed that one of two Regeneron antibodies was less effective against the South African virus mutation, but the two-antibody cocktail maintained its effectiveness. [115]

Constraints on Therapeutics

Accessibility presupposes availability, which raises the challenge of supply. Our earlier paper laid out several challenges related to manufacturing capacity that must be addressed for antibodies to be made available at scale. Both Lilly and Regeneron moved non-Covid-19 mAbs to sites in Europe and signed deals with major manufacturers (Lilly teamed up with Amgen and Regeneron worked with Roche) to increase production in the US, facilitating the production of between 6 million and 7 million doses for this year. [116] Although Covid-19 vaccines are being rolled out, major quantities of antibodies will still be needed for those who cannot take vaccines in addition to those needing treatment.

Access to critical biologics is now a national security issue, especially given that future pandemics will emerge that require such medicines. Data from the CPHi Annual report underscore the trends in biologics supply and demand that will require strategic engagement between governments, drug companies, and manufacturers in order to ensure stable supply. While short-term pressures are beginning to ease, the landscape from 2024 on reveals that manufacturing capacity will be a problem, driven by "the progress of Alzheimer's drugs, PDL/PDL-1 checkpoint inhibitors and COVID-19 therapeutics currently in late stage development" – which translates into "global biomanufacturing capacity [that] is expected to increase to 6500kL by 2024 at a CAGR of 6.4 percent – up from 4700kL in 2019 – but capacity demand is rising faster and will reach 4700kL in 2024 at a CAGR of 12 percent." [117]

Additional findings lay bare the gap between reactor capacity that is coming onstream and what is actually required to meet future demand.

"Only 20 percent of the new bioreactors projected by 2024 will be of 10,000L size, while 50 percent will be of 2000L scale . . . [T]he most probable scenarios will see half of Phase II and III products requiring a bioreactor capacity of 10,000L to meet demand – and COVID-19 products will undoubtedly require multiple large-scale bioreactors . . . [T]he challenge here is that much of the new bioreactor installations reflect a pre-pandemic demand profile. In terms of access, currently around 70 percent of bioprocessing capacity is owned by product developers, with contract manufacturing organisations (CMOs) and hybrid companies providing the remainder. [T]his potentially means innovators without in-house manufacturing may have difficulty accessing capacity as their products move towards commercial scale . . . [T]he distribution of capacity will continue to change over the next four years, with CMO/hybrid capacity share increasing to 36 percent. In terms of geographic spread of capacity, Europe will equal North America for total biomanufacturing capacity by 2024, with Asia also expanding." [118]

Governments are in a position to undertake stop-gap measures to ease the pressure in the near-term. [119] First, governments can assume the financial risk for companies that are willing to take on the role of contract manufacturer for Covid-19 antibodies. Second, governments could also pay them to have access to their manufacturing space, guaranteeing production. Third, governments could pay companies a premium to purchase and stockpile antibodies; and they could also be paid to license them. Finally, governments could preserve the active pharmaceutical ingredient (API) in antibodies by freezing a portion of it and storing it until it is need. Drug companies do this now, as API remain stable for at least three years at freezer temperatures; thawing the drug and making it into a finished medicine can be done in under a month. Such actions must be accompanied by longer-term, public-policy-derived strategies to ensure onshore manufacturing capacity. Collaboration across the biologics value chain, with government providing an enabling environment, reducing risk and facilitating coordination from research and development through to fast-tracked, streamlined regulatory approval and distribution are required to meet the challenge.

Concluding Reflections

One year into the Covid-19 pandemic the reality remains that therapeutics will continue to be an important part of managing the crisis. . Promising drugs are making their way through clinical development, including those that can be given before hospitalisation is required. For these to be effective, seamless coordination of testing and administering of the treatments will be critical. These drugs will matter greatly not just for rich countries, but for LMICs that lack the necessary infrastructure and regulatory mechanisms to make antivirals and mAbs easily available and accessible. For these drugs to be fully effective, the global health architecture will need significant reform, as the pandemic has laid bare its weaknesses. Lack of global coordination has undermined bringing desperately needed drugs to market quickly. It has also shown itself in the inability to properly aggregate demand for Covid-19 medical products and procure them at scale for LMICs. The procurement of 2.9 million courses of dexamethasone is a positive development, but in the absence of the accompanying oxygen that is required, it is insufficient to the task. Better connections between country needs and global procurement mechanisms are required, as is additional funding. It is in the interest of rich countries to support pandemic containment in LMICs, as the proliferation and spread of mutations has made obvious that pandemic anywhere is pandemic everywhere. Finally, governments must confront the national security threat that the lack of biologic capacity poses. Piecemeal efforts may help them muddle through the current pandemic but will not be sufficient in the face of new pandemics that will most certainly arise. Public policy domestically and globally must urgently address these problems in order for peace, prosperity and good health to be experienced by all.

Annex

Table 1 – Drugs under clinical development to treat Covid-19

Drug	Developer/ Researcher	Sponsor	Phase	Type/Target family
Pepcid (famotidine)	Yamanouchi Pharmaceuticals; J&J; Merck	Northwell Health	Phase III	**H2 blocker**
Bucillamine	Revive Therapeutics, LTD		Phase III	Anti-rheumatic agent
Lenzilumab	Humanigen; Catalent	NIAID	Phase III	Monoclonal antibody
Ilaris (canakinumab)	Novartis	Novartis	Phase III	Monoclonal antibody
Farxiga (dapagliflozin)	Bristol-Myers Squibb Astra Zeneca	AstraZeneca	Phase III	Oral sodium-glucose co-transporter 2 (SGLT2) inhibitor

Drug	Developer/ Researcher	Sponsor	Phase	Type/Target family
Ultomiris (ravulizumab)	Alexion	Alexion	Phase III	Monoclonal antibody
Losmapimod	Fulcrum Therapeutics	Fulcrum Therapeutics	Phase III	Mitogen-activated protein kinase (MAPK) inhibitor
Metformin (Glucophage, Glumetza, RIomet)	University of Minnesota	University of Minnesota	Phase II/III	Biguanide
Niclocide (niclosamide)	ANA Therapeutics	Tufts Medical Center; First Wave Bio, Inc; Lille University Hospital	Phase II/III	Anthelmintic
Velklury (remdesivir)	Gilead Sciences	Gilead Sciences	Phase II/III	Antiviral
PTC299	PTC	PTC	Phase II/III	Dihydroorotate Dehydrogenase (DHODH) inhibitor

Drug	Developer/ Researcher	Sponsor	Phase	Type/Target family
RLF-100 (aviptadil)	NeuroRx; Relief Therapeutics	NeuroRx	Phase II/III	Synthetic human vasoactive intestinal peptide (VIP)
Actemra (tocilizumab)	Roche		Phase III	IL-6 receptor agonist
ABX464	Abivax	Bpifrance	Phase IIb/III	HIV-1 Rev protein inhibitor
Rhu-pGSN (gelsolin)	BioAegis Therapeutics	Unknown	Phase II	Recombinant human plasma
EIDD-2801, oral ribonucleoside analog	DRIVE; Ridgeback Biotherapeutics; Merck	Unknown	Phase II	Antiviral
LAM-002A (apilimod dimesylate)	AI Therapeutics, Inc;	AI Therapeutics, Inc.; Yale University	Phase II	PIKfyve Inhibitor

Drug	Developer/ Researcher	Sponsor	Phase	Type/Target family
Convalescent plasma	Multiple	Multiple	Phase I/ Phase II	Immunoglobulin
AdMSCs	Celltex Therapeutics	Celltex Therapeutics	Phase II	Autologous adipose-derived stem cells
Remicade (infliximab)	Janssen	UHB; Birmingham National Institute for Health Research Biomedical Research Centre; NIHR BRC)	Phase II	Monoclonal antibody
Gimsilumab	Rolvant Sciences	Rolvant Sciences	Phase II	Monoclonal antibody
Otilimab	MorphoSys; GSK	GSK	Phase II	Monoclonal antibody
STI-5656 (abivertinib)	Sorrento Therapeutics		Phase II	Tyrosine kinase inhibitor

Drug	Developer/ Researcher	Sponsor	Phase	Type/Target family
Humira (adalimumab)	University of Oxford	Covid-19 Therapeutics Accelerator	Phase II	Anti-TNF
COVI-GUARD (STI-1499)	Sorrento Therapeutics	Sorrento Therapeutics	Phase I	Monoclonal antibody
JS016	Lilly; Junshi Biosciences	Lilly	Phase I	Monoclonal antibody
DNL 758 (SAR443122)	Sanofi/Denali Therapeutics	Sanofi	Phase Ib	RIPK1 inhibitor
REGN-COV2	Regeneron	Regeneron	Phase I/II/III	Antibody cocktail
PTC299	PTC	PTC	Phase II/III	Dihydroorotate dehydrogenase (DHODH) inhibitor
LY-CoV555	Lilly;AbCellera	Lilly; Operation Warp Speed	Phase I/II/III	Monoclonal antibody

Source: Tracker is taken from "Covid-19 therapeutics tracker," Regulatory Focus, updated 21 August 2020, available at https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-therapeutics-tracker"

Table 2 – Clinical studies evaluating anti-SARS-CoV-2 monoclonal antibodies

Sponsor	Drug Code	Status	Estimated Start Date	Estimated Primary Completion
Jemimcare Group	JMB2002	N/A	N/A	N/A
Bristol-Myers Squibb and Rockefeller University	C144-LS and C-135-LS	Phase I	11/1/21	June 2021
AbbVie	ABBV-47D11	Phase I	27/11/20	August 2021
HiFiBiO Therapeutics	HFB30132A	Phase I	October 2020	July 2021
Ology Bioservices	ADM03820	Phase I	4/12/ 2020	September 2021
Beigene	DXP604	Phase I	15/12/ 2020	March 2021

Hengenix Biotech Inc	HLX70	Phase I pending	9/12/2020	September 2021
CORAT Therapeutics	COR-101	Phase I/II pending	31/1/2021	April 2021
U. Cologne/Boehringer Ingelheim	BI767551	Phase I/II	23/11/2020	30/6/2021
	DZIF-10c		23/11/2020	30/6/2021
Junshi Biosciences/Eli Lilly and Company	JS016	Phase I	5/6/2020	12/2020
	LY3832479		19/6/2020	2/10/2020
	LY-CoV016		17/6/2020	11/3/2021
Tychan Pte. Ltd	TY027	Phase III	9/6/2020	10/2020
			4/12/2020	31/8/2020
Brii Bioresources	BRII-196	Phase I	12/7/2020	

Brii Biosciences	BRII-198	Phase I	13/7/2020	
Sinocelltech Ltd	SCTA01	Phase I	24/7/2020	
Sorrento Therapeutics, Inc	COVI-GUARD (STI-1499)	Phase I	17/9/2020	
Mabwell (Shanghai) Bioscience Co., Ltd.	MW33	Pivotal Phase II	7/8/2020 11/2020	12/2020 May 2021
Sorrento	COVI-AMG (STI-2020)	Phase I/ Phase II pending	December 2020	April 2021
Hengenix Biotech Inc	HLX70	Phase I Pending	9/12/2020	September 2021
Beigene	DXP593	Phase II Pending	31/8/2020 30/10/2020	15/10/2020 28/2/2021

AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Phase III	17/8/2020 17/11/2020 16/11/2020	9/2021 2/2022 1/2022
Celltrion	CT-P59	EUA#	18/7/2020 4/9/2020 25/9/2020	11/2020 23/12/2020 12/2020
Vir Biotechnol./ GlaxoSmithKline	VIR-7831/ GSK4182136	Phase II/ Phase III	27/8/2020 TBD	January 2021 TBD
AbCellera / Eli Lilly and Company (EUA in the US)	LY-CoV555 (LY3819253) combination of LY-CoV555 with LY-CoV016 (LY3832479) EUA*	Phase I Phase II Phase III Activ-3 study Phase II/ III	28/5/2020 13/6/2020 2/8/2020 4/8/2020 August 2020	23/8/2020 15/9/2020 8/3/2021 July 2021 February 2021

Regeneron (EUA in the US)	REGN-COV2	Phase I/II	16/6/2020	19/12/2020
		Phase I/II		25/1/2021
	REGN10933 + REGN10987	Phase III	10/6/2020	15/6/2021
			13/7/2020	13/3/2021

#EUA granted in South Korea

*EUA granted in the US

Source: "Covid Biologics Tracker", Antibodies Society

Footnotes

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