TONY BLAIR
INSTITUTE
FOR GLOBAL
CHANGE

Therapeutics and Covid-19: The Global Race for an Effective Treatment

EVA THORNE

Contents

Published at https://institute.global/policy/therapeutics-and-covid-19-global-race-effective-treatment
on May 27 2020

[Note: We published an update to this paper on 21 August 2020, "Therapeutics and Politics: The Evolving Covid-19 Treatment Landscape"]

This paper presents a synthesis of the Covid-19 treatment literature, with a focus on what is happening both in the UK and globally. It covers several issues that have political and public policy ramifications for government leaders and international institutions. The cross-cutting theme is that a lack of coordination around the clinical development, approval and eventual production and distribution of therapeutics hampers their efficacy. This has profound and potentially negative implications for both public health and politics. The paper covers the following:

- The treatment landscape of the UK and elsewhere, including the types of drugs under clinical development; what seems promising; and some discussion of the disjuncture between therapeutics approved for limited use and grey and off-label use 'on the ground' in a range of countries.
- The landscape of clinical trials globally, which is characterised by fragmentation, lack of coordination among critical stakeholders – especially political leaders – and mixed results, which could delay approval of drugs.
- The potential tensions between pharmaceutical companies and governments with respect to issues such as availability, pricing and accessibility.

Recommendation: Global Coordination Among Political Leaders, Researchers and Pharma is Key

The Covid-19 pandemic has led to a global race to find effective treatments. The failure to establish a global framework for coordination and cooperation at the political level (heads of government) has had significant, negative and unintended consequences.[1] First, there is a spike in the unauthorised sale and use of drugs such as hydroxychloroquine and chloroquine, which makes them less available for non-Covid-19 patients who depend on them to treat chronic diseases. Second, improper usage of potentially effective drugs threatens global supply and distribution chains. Third, multiple and often redundant clinical trials trigger inefficiencies that undermine the generation of conclusive results necessary for approval of treatments. Finally, the lack of coordination risks undermining access of any approved treatments for poorer countries, as rich countries will likely focus on their own populations.

The centralised coordination of the full lifecycle of Covid-19 treatment development activities is (urgently) needed. Coordination should have two components. The first would aggregate and disseminate data collected from national drug regulatory bodies. Second, this would create a central repository of data on clinical trials and 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; [2]
- Other relevant data that may indicate potential problems, as an early warning system

These are the types of issues that are more amenable to political decision-making. There are complex realities of how pharmaceutical companies and clinical development function. At that 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 World Health Organisation (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.[3]

Geopolitics are already present in global discussions around access to treatments and vaccines in the absence of a global leader. There is a proliferation of proposals for pools to aggregate intellectual property (IP), such as the voluntary agreement proposed by the President of Costa Rica: the Medicine Patent Pool (MPP), with funding from Unitaid, which has expanded its mandate to take on the proposal. The objective is to prevent lack of access to affordable treatment and vaccines, and to promote collaboration in the development and production of Covid-19 products. The pool provides access to various forms of IP rights – including patents – for items such as drugs, vaccines and medical technologies. The global agreement could coordinate key stakeholders around prioritising approved therapies, building production capacity, pricing, accessibility and organised rollout. The Costa Rican president publicly stated his commitment to opening the pool later this month.

European leaders have called for open and equitable access to treatments and vaccines. On 24 April 2020 the UK government pledged that it would support global access to Covid-19 vaccines and therapies.[4] Despite this, the UK, Switzerland and the US, along with others, have opposed the WHO leading the call for open licensing for Covid-19 products. A British government spokesperson, ahead of the vote on the resolution, stated that "The UK has long supported affordable and equitable access to essential medicines, including in low and middle-income countries. We continue to support public-private partnerships for product development, and approaches such as non-exclusive voluntary licensing which promote affordable access for all while also providing incentives to create life-changing vaccines."[5] The pharmaceutical trade body, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), points out that a number of such voluntary pools exist with industry participation, that a new platform risks diverting energy and resources from important objectives and that weakening intellectual

1 Some regulatory institutions have collaborated with pharmaceutical companies during the pandemic. This is different from the level of heads of government, whose involvement could address various bottlenecks.

2 Paul N. Newton, Katherine C. Bond, et. al., "Covid-19 and risks to the supply and quality of tests, drugs, and vaccines," The Lancet, 9 April 2020, https://doi.org/10.1016/S2214-109X(20)30136-4.

property is counterproductive.[6] Again, the proliferation of proposals underscore the absence of political leadership and coordination.

3 Ibid.

4 UK government press release, "UK leads way as national endorse landmark pledge to make coronavirus vaccines and treatments available to all," 24 April 2020, https://www.gov.uk/government/news/uk-leads-way-as-nations-endorse-landmark-pledge-to-make-coronavirus-vaccines-and-treatments-available-to-all

5 Sara Boseley, "US and UK 'lead push against global patent pool for Covid-19 drugs,'" The Guardian, 17 May 2020, https://www.theguardian.com/world/2020/may/17/us-and-uk-lead-push-against-global-patent-pool-for-covid-19-drugs

6 Ibid.

The Context: Treatment as a Way to Support Rebooting the Economy

A wide range of countries – including the UK, the US, Italy, India, South Africa and Ghana – have implemented some form of lockdown in order to stop the spread of the highly contagious, communicable novel coronavirus. As the days in lockdown have increased, some of these countries' economies have plunged into deep recession, some with unemployment levels that exceed those seen during the Great Depression. Businesses have collapsed, many never to return; food shortages and hunger are increasingly common; and the decline in revenue and taxes will affect public services, including those for health, for years to come. Governments with the fiscal space to do so have stepped in with relief and stimulus packages. Whether political leaders say so explicitly or implicitly, they understand that their economies simply cannot sustain current or future lockdowns for extended lengths of time. They are therefore faced with a dire situation: They must carefully calibrate saving lives with saving their economies – and both are connected, it is not one or the other. Many political leaders are navigating and balancing this tension with public policies that include mass testing, tracing and isolation, and mandatory masks to allow economic activity to resume. These are significant elements of what is necessary for some semblance of normalcy to return.

To date, vaccines have received significant attention as they are the ultimate solution to the challenge of dealing with the Covid-19 pandemic. Despite the global race to find a vaccine, it is conventional wisdom that one will not be available until sometime in 2021 – a timeline which assumes no glitches in the development and production processes. Recent scientific breakthroughs for a vaccine are promising. The University of Oxford and UK pharmaceutical company AstraZeneca began Phase 1 human testing of a vaccine in early April, with results due in either June or July.[7] Developing production capacity for any viable vaccine and then manufacturing on a global scale will take some time, even though some companies have put production capacity in place in anticipation of success. Once a vaccine is ready, the politics and economics of distribution and access will come into play and challenges will be inevitable.

Parallel efforts are underway to identify and approve therapeutics to treat Covid-19. To date, only a few are approved for treatment: Veklury (remdesivir) in Japan, and Avigan (favilavir) in both Italy and China.[8] In Japan, Prime Minister Abe recently fast-tracked a review of Avigan, which would speed up the approval process by months.[9] On 26 May 2020, UK

regulators approved remdesivir for use on certain hospitalised patients. Treatment options must assume greater importance, along with mass testing, tracing, isolation, social distancing and wearing masks in public. While not panaceas, treatments hold the promise of keeping people from dying; out of hospital intensive care units (ICUs) and off wards; and from suffering protracted periods of time with debilitating symptoms. As such, they shorten the period of illess and enable people to resume their daily lives, including economic activity. With governments fast-tracking licensing and approval processes, such therapeutics could become widely available well ahead of vaccines, transforming death sentences and severe illness into milder infections that are manageable.

This paper engages the key issues around Covid-19 therapeutics that senior political leaders and international institutions must address to ensure that therapeutics can be approved and delivered at scale in ways that: do not undermine their availability for other diseases; ensure they are affordable for and accessible to poor countries; ensure that they are quality-assured. Key issues that emerge from a review of the therapeutics landscape include:

- Multiple, fragmented, mixed-quality clinical trials of existing, approved drugs that produce inconclusive results, thereby lengthening the time to potential approval of desperately needed treatments. The WHO, which has a mega-trial of approved drugs, is just one of many players in the space.
- Limited number of clinical trials taking place in under-resourced health systems in Africa. Context-specific trials would be sensitive to issues of relevance, affordability, drug availability, adaptability and ease of administration.
- The proliferation of a grey and black market in certain drugs that limits their availability to treat other diseases. Pronouncements by political leaders have exacerbated this trend.
- Competing pressures that affect cost and access of any approved drugs, as governments seek to secure therapeutics for their populations and

7 Lina Saigol, "AstraZeneca teams up with Oxford University to develop coronavirus vaccine – first results from human trials expected in June or July 2020, Marketwatch, 3 May 2020, https://www.marketwatch.com/story/astrazeneca-teams-up-with-oxford-university-to-develop-coronavirus-vaccine-first-results-from-human-trials-expected-in-june-or-july-2020-04-30

8 Jeff Craven, "Covid-19 therapeutics tracker," Regulatory Force, 8 May 2020, https://www.raps.org/news-and-articles/news-articles/2020/3/Covid-19-therapeutics-tracker

9 Juntaro Arai and Rina Mitsutake, "Avigan set for approval this month in Japan as coronavirus drug," Nikkei Asian Review, 5 May 2020, https://asia.nikkei.com/Business/Pharmaceuticals/Avigan-set-for-approval-this-month-in-Japan-as-coronavirus-drug

drug companies seek profitability. What is currently a trickle of compulsory licensing could become a deluge in the absence of a unified mechanism/global agreement to address IP rights so as to ensure access and affordability. Where public money has contributed to drug development, this issue takes on added political dimensions.

Addressing these challenges requires a coordinated approach, which has proven difficult in the absence of a hegemon (formerly the US) that is able to lead by example, set the agenda and convene. Regional political leadership and a proliferation of public-private partnerships have emerged, but a lacuna still exists that could be filled by global cooperation. This requires leadership by governments and a recognition that going it alone is counter-productive.

Therapeutics: The Lay of the Land

Ongoing global research to develop treatments for the virus falls into three categories:

1. Drugs already approved and publicly available for treatment of other diseases that are being tested for treatment for Covid-19
2. Drugs that have shown promise in animal studies for treating severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)
3. New research (pre-clinical trial) to develop new drugs and approaches (these will take the longest to develop)

The first category includes drugs such as: Lopinavir/Ritonavir (currently authorised as an anti-HIV medicine); chloroquine and hydroxychloroquine (currently authorised as treatments against malaria and certain auto-immune diseases such as rheumatoid arthritis); and systemic interferons and, in particular, interferon beta (currently authorised to treat diseases such as multiple sclerosis). The second category includes remdesivir (an investigational, anti-viral compound).

The last category (new research, pre-clinical trials) includes the use of antibodies, which are present in the blood plasma (a clear liquid that carries platelets, red and white blood cells throughout the body) of people who have recovered from the virus. The plasma from individuals who have recovered from a disease is referred to as convalescent plasma (CP) as it contains the relevant antibodies to fight the disease. These antibodies can be harvested to use in a plasma treatment or can be used for the basis of developing recombinant monoclonal antibodies. A number of companies are taking this approach. Possibly the most promising one is the cocktail approach of Regeneron.

An antibody-based approach to Covid-19 is viewed by many in the science community as a bridge to a vaccine; a number of pharmaceutical companies have begun or are preparing to trial such drugs. The recombinant monoclonal approach requires full clinical development, which extends the timeline significantly compared to the other two categories. The process for plasma treatments is more immediate. There are two approaches with plasma: direct transfusion of CP, which is available today or further manufacturing of the CP to make an investigational hyperimmune globulin, a drug with a purified and concentrated level of disease-specific antibodies, which will begin trials this summer. Both approaches require donations of CP. The UK is currently trialling whether convalescent plasma could be

used to treat those who are seriously ill with Covid-19; more than 6,500 people are participating and trials elsewhere are underway.[10]

Due to the urgency of developing a treatment and the limited amount of CP available, traditional competitors have turned into collaborators, with companies such as Japan-based Takeda working with CSL Behring in in the US, Biotest, BPL, LFB and Octapharma, with support from companies like Microsoft, Uber Health and others. The CoVig-19 Plasma Alliance – an initiative launched by Takeda's Plasma-Derived Therapies Business Unit – is focused on sharing resources (especially plasma), to accelerate drug development and supply. The Alliance operates more than 500 plasma collection centres in the US, with additional collection facilities in Austria, Czechia, Germany and Hungary.[11]

Therapeutics in the UK

There are currently no approved therapeutic drugs to treat the general public for Covid-19 in the UK; there is limited, emergency approval for one. The need for effective treatment for patients suffering from the disease is high given the fact that one in seven patients hospitalised with the virus die; about 50 per cent of ICU patients eventually die. The UK controls the supply of drugs that appear to be relevant for managing Covid-19, many of which are also used to manage other diseases; they are being prescribed for trials and are discouraged for use outside such research.

The UK government, through its National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI), has provided £20 million in funding "for research projects that will contribute to our understanding, diagnosis, prevention or management of coronavirus."[12] The call for proposals covers two categories, one of which is vaccines and therapeutics. The fund closed on 13 February with results expected in 18 month or fewer. Given the overwhelming burden on hospitals and the economy in the UK (and elsewhere), development of treatments for Covid-19 is critical. (See Table 1 for all the trials underway.) Regulatory authorities have fast-tracked the process for bringing drugs to market because of the scale of the pandemic.

In the case of the UK, research funds are focused on supporting projects that show the potential for rapid development: "[r]e-purposing of existing therapeutics, e.g. proteases, helicases or entry inhibitors; development of mAbs or other biologics."[13] A full list of therapeutics under evaluation in

the UK through its special fund is attached in the Annex. Most trials are of existing and approved drugs.

On 29 April 2020, the UK government, through its Department of Health and Social Care, announced the creation of an innovative platform that allows for Covid-19 treatments to be fast-tracked through a new national clinical trial initiative. ACCORD (Accelerating COVID-19 Research & Development platform) "aims to get an early indication of drug treatments' effectiveness in treating coronavirus and if positive results are seen, these drugs will advance rapidly into the large-scale trials currently in progress across the country…" It has three features:

- Rapidly scaled-up national initiative will mean clinical trials could start in weeks rather than months
- Six drugs entering clinical trials as part of national effort made possible by government, academia and industry working together
- This will give an early indication of whether these drugs could save lives and improve the outcomes of the most vulnerable patients with Covid-19[14]

Promising drugs will then be channelled into the UK's RECOVERY trial, which, at the time of writing, is the world's largest randomised controlled trial for Covid-19 treatments. The first drug selected is Bemcentinib (which blocks viral entry), created by Norway-based BerGenBio ASA, a clinical-stage biopharmaceutical company.[15]

Regulatory Hurdles

There is strong evidence that convalescent plasma holds promise as a Covid-19 treatment. With respect to the UK, however, existing regulations pose a challenge to domestic production of any blood plasma-derived therapy that eventually receives approval. Regulatory change resulted from

10 Catherine Burns and Rachael Buchanan, "Coronavirus: thousands signal interest in plasma trial," BBC News, 2 May 2020, https://www.bbc.co.uk/news/health-52510865

11 Takeda Newsroom, "Working together to go faster for patients," 18 April 2020, https://www.takeda.com/newsroom/featured-topics/working-together-to-go-faster-for-patients/

12 National Institute for Health Research, "NIHR and UKRI launch £20 million funding call for novel coronavirus research," 4 February 2020, https://www.nihr.ac.uk/news/nihr-and-ukri-launch-20-million-funding-call-for-novel-coronavirus-research/23942

13 Ibid.

the mad cow disease (bovine spongiform encephalopathy - BSE) outbreak that gripped the UK in the mid-2000s and resulted in the deaths of three people who received infected blood transfusions. Transfusion-acquired variant Creutzfeldt-Jakob disease (vCJD) caused the deaths. Production of immunoglobulins derived from British blood plasma donors was banned in 2004. Imported plasma was used for treatments for people born after 1 January 1996, with plasma supplies sourced from countries with a donor population at lower risk of carrying CJD than the UK population and with comparable safety regulations. Austria and Poland provide England with about 10 per cent of its blood plasma supply, some of which is imported by other UK nations.[16] Britons born after 1 January 1996 would not have been exposed to the disease through the food supply chain. As a result, in 2019 the UK government overturned the ban on the use of blood plasma for direct transfusions in patients born after this date. Despite these changes, a ban on using UK plasma for manufacturing plasma protein therapy remains. Importantly, this means that the UK does not have the supply of blood plasma that it would need to produce a treatment for Covid-19 or for other rare diseases that are treated effectively with plasma-derived immunoglobulins. If a treatment is approved, then a global race for blood plasma likely will result and the UK will be behind in the scramble for a secure supply. This is not just a public health emergency but potentially also a national security one, given the high potential for government action to forcibly (but legally) secure supplies within the pharmaceutical value chain.

The Use of Therapeutics on the Ground: Remdesivir, Chloroquine and Hydroxychloroquine

Despite official regulations, the evidence clearly shows that use of various drugs outside these approved channels is proliferating. The consequences are significant and include: unsafe use; hoarding and lack of availability of the drugs to treat other diseases; and the potential for sub-standard and fake drug production.

14 UK government press release, "COVID-19 treatments could be fast tracked though new national clinical trial initiative," 29 April 2020, https://www.gov.uk/government/news/Covid-19-treatments-could-be-fast-tracked-through-new-national-clinical-trial-initiative

15 For more information about the drug and the trial, see the cover letter from the company's CEO about the clinical trial: https://www.bergenbio.com/ceo-letter-Covid-19-clinical-trial/

16 Reality Check team, "Contaminated blood scandal: where does the UK's blood supply come from?" BBC News, 28 September 2018, https://www.bbc.co.uk/news/health-45641186

Remdesivir

On 29 April 2020, Gilead Sciences, Inc. announced the results from its government-sponsored (National Institute of Allergy and Infectious Diseases – NIAID), open-label, Phase III SIMPLE trial of the anti-viral drug, remdesivir, which studied 5-day and 10-day dosing of hospitalised patients who were severely ill with Covid-19 disease.[17] The drug reduced the length of symptoms from 15 to 11 days (31 per cent); it is unclear whether the drug's effect on mortality rates is significant. These are the most conclusive, positive results from a clinical trial of the drug. On 2 May 2020, the US Food and Drug Administration (FDA) approved the use of remdesivir on an emergency basis for treating people hospitalised with Covid-19. Japan followed on 7 May 2020, approving remdesivir for use in severely ill Covid-19 patients. The UK government announced a collaboration with Gilead Sciences to test remdesivir on Covid-19 patients who could most benefit from the drug.[18] It is unclear how many patients will receive the drug. The WHO will discuss with the American government and Gilead Sciences, Inc. how to make the drug more widely available, even as the global health organisation continues testing the drug as part of its SOLIDARITY mega-trial. Full results from the NIAID were released and published in the New England Journal of Medicine on 22 May 2020

Chloroquine and Hydroxychloroquine

With respect to the highly-touted drug chloroquine and its derivative, hydroxychloroquine, the evidence from clinical trials is often inconclusive and sometimes negative with more studies showing significant problems.[19] In response to concerns over the drug's safety, the WHO temporarily halted clinical trials of hydroxychloroquine, which have been part of the global health organisation's SOLIDARITY mega-trial of various Covid-19 treatments, even as the US President Donald J. Trump claimed to be taking the drug prophylactically.[20] A study of chloroquine in Brazil, for example, was stopped in April as a high dose led to several deaths. However, a small, positive (yet inconclusive) trial in China of hydroxychloroquine and a controversial trial in France have fuelled popular demand for the drug. Notwithstanding these problematic trials, data indicate widespread global use of both drugs (as well as remdesivir). The health-care data company, Sermo, conducted a global survey of 5,000 physicians. Forty-four per cent prescribed hydroxychloroquine for Covid-19 patients and 38 per cent believed it to be effective, with a similar percentage responding that remdesivir was effective; data suggest better efficacy outside hospital settings.[21] The US Food and Drug Administration (FDA) has approved the two drugs for emergency use for a small number of hospitalised Covid-19 patients; and doctors in France and Italy can prescribe the drugs. In both the US and France, warnings about side effects have also been issued. Use

of hydroxychloroquine is permitted in India by frontline health workers and, in instances where someone in the same living quarters has the virus, doctors must provide prescriptions. Hospitals in Burkina Faso, Cameroon and South Africa are authorised to use chloroquine; 50 per cent of those with the infection in Senegal are being treated with hydroxychloroquine; and Felix Tshisekedi, president of the Democratic Republic of the Congo, urged rapid, industrial-scale production of chloroquine.[22]

Hydroxychloroquine and chloroquine also are being used to treat Covid-19 in the US, boosted (and arguably, globally) in part by the public pronouncements of President Donald J. Trump. Data provided by IPM.ai and obtained by The New York Times shows that retail pharmacies in the US received first-time prescriptions (nearly 32,000) for the two drugs at a rate of 46 times the rate of the average weekday.[23] As the chart published by the newspaper shows (see graph below), the surge happened immediately after President Trump's press conference on 19 March 2020 where he touted the potential of the two drugs to alleviate coronavirus symptoms. ProPublica, the investigative journalism organisation, found that the shortage of the two anti-malarial drugs in the US is due partially to pharmacists and doctors prescribing them for friends, families and themselves in defiance of federal guidelines.[24] The ProPublica analysis was informed by interviews with pharmacists and state regulators, who pointed out that in some instances outright fraud underpinned the prescriptions that were written. Hoarding was not uncommon. The Association of

17 "Gilead announces results from phase-3 trial of investigational antiviral Remdesivir in patients with severe Covid-19," 29 April 2020, https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-Covid-19

18 "Coronavirus live news: global cases pass 5.5 million as WHO warns of 'second peak,'" The Guardian, 26 May 2020, https://www.theguardian.com/world/live/2020/may/26/coronavirus-live-news-covid-19-uupdates-who-drops-hydroxychloroquine-trial-as-mexico-death-toll-questioned

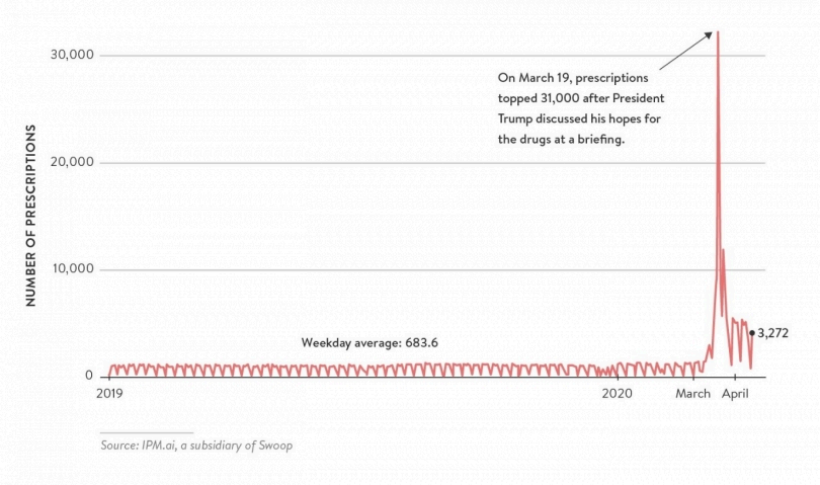
19 Chloroquine and hydroxychloroquine are anti-inflammatories, which help counter over-active immune systems, that may be effective in treating Covid-19. The efficacy of the drugs depends on when in the lifecycle of Covid-19 infection they are used. Antiviral drugs are likely to be most effective when administered as early as possible – perhaps even as a preventative – while anti-inflammatory drugs could be damaging if used too early as they could weaken the immune system's response.

20 "Coronavirus: WHO halts trials of hydroxychloroquine over safety fears," BBC, 25 May 2020, https://www.bbc.co.uk/news/health-52799120

21 Sermo press release, "Sermo reports jury is still out on Remdesivir; 31% of physicians who have used Remdesivir rate it as highly effective; 38% rate it as somewhere in the middle," 23 April 2020, https://www.sermo.com/press-releases/sermo-reports-jury-is-still-out-on-remdesivir-31-of-physicians-who-have-used-remdesivir-rate-it-as-highly-effective-31-rate-it-with-low-effectiveness-38-rate-it-as-somewhere-in-the-middle/; also cited in Alice Park, "Vaccines, antibodies and drug libraries. The possible Covid-19 treatments researchers are excited about," Time, 14 April 2020, https://time.com/5819965/coronavirus-treatments-research/

American Physicians and Surgeons (AAPS) wrote a letter to Arizona's governor, Doug Ducey, requesting that he rescind the executive order forbidding the prophylactic use of the two drugs without peer-reviewed data.[25]

Figure 1 – A Surge in First-Time Prescriptions for Chloroquine and Hydroxychloroquine



In contrast to the US, British regulators have limited the use of hydroxychloroquine and chloroquine to clinical trials. However, the charity Lupus UK has received telephone calls from concerned lupus patients, who depend on hydroxychloroquine to treat the auto-immune disease, about the drug not being available at pharmacies.[26] Other governments have moved to restrict access to hydroxychloroquine and chloroquine because of widespread hoarding: Kuwait limits their use to health centres and hospitals after withdrawing medicines that contain them from private pharmacies; Jordan's pharmacies can no longer sell hydroxychloroquine in an effort to prevent hoarding; and Kenya allow the use of chloroquine only with a prescription, after having banned over the counter sales.[27] In March, India – the world's largest manufacturer of hydroxychloroquine – temporarily banned exports of the drug and also made it available only with a prescription; France has banned exports of chloroquine and Morocco has

22 Agence France-Presse, "Africans rush for chloroquine as coronavirus tsunami looms," South China Morning Post, 2 April 2020, https://www.scmp.com/news/world/africa/article/3078039/africans-rush-chloroquine-coronavirus-tsunami-looms

23 Ellen Gabler and Michael H. Keller, "Prescriptions surged as Trump praised drugs in coronavirus fight" New York Times, 25 April 2020, https://www.nytimes.com/2020/04/25/us/coronavirus-trump-chloroquine-hydroxychloroquine.html.

24 Topher Sanders, David Armstrong, and Ava Kofman, "Doctors are hoarding unproven coronavirus medicine by writing prescriptions for themselves and their families," ProPublica, 24 March 2020, https://www.propublica.org/article/doctors-are-hoarding-unproven-coronavirus-medicine-by-writing-prescriptions-for-themselves-and-their-families

requisitioned it.[28] The situation is the same in Southeast Asia, where pharmacies in Indonesia, Myanmar and Vietnam have been deluged with requests for chloroquine, which requires a prescription but can be purchased in a region with lax regulation.[29] In Libreville, Gabon, a lupus advocate monitors supplies of chloroquine at the city's only pharmacy that has any chloroquine left, while journalists report high demand at pharmacies in Abidjan, Ivory Coast; Luanda, Angola; and in Malawi.[30]

Usually companies have strong quality compliance and recalls standards in place but, in certain instances, rising demands for such drugs may trigger an increase in low-quality (because of mistakes in supply chains and production) and fake drugs (driven by outright fraud), further imperilling lives. The former occurs because of cost-cutting measures while the latter is due to scarcity and flourishes when desperate people purchase from the grey and black markets.[31] There is already evidence of fake drugs entering the market in developing countries, with regulatory authorities issuing warnings to consumers.

Other therapeutics in use on the ground. The same Sermo survey found Azithromycin (an antibiotic used to treat various infections) and bronchodilators to be among the top three drugs used (along with hydroxychloroquine) to treat Covid-19 patients. While not commonly in use, physicians perceived convalescent plasma to be the most effective as compared to other treatments in all settings: non-hospital, hospital and ICU. (See Table 2 for Sermo's table of drugs viewed as effective by physicians surveyed.) This is in keeping with efforts by the CoVIg-19 Plasma

25 "AAPS letter asking Governor Ducey to rescind executive order concerning hydroxychloroquine in COVID-19," 27 April 2020, https://aapsonline.org/aaps-letter-asking-gov-ducey-to-rescind-executive-order-concerning-hydroxychloroquine-in-Covid-19/ A key passage is worth quoting at length: "Attached and posted here (https://bit.ly/cqhcqresearch) is a summary of peer-reviewed evidence, indexed in PubMed, concerning the use of CQ and HCQ against coronavirus. We believe that there is clear and convincing evidence of benefit both pre-exposure and post-exposure. In addition, Michael J. A. Robb, M.D., of Phoenix is compiling all reports as they come in. As of this date, the total number of reported patients treated with HCQ, with or without azithromycin and zinc, is 2,333. Of these, 2,137 or 91.6 percent improved clinically. There were 63 deaths, all but 11 in a single retrospective report from the Veterans Administration where the patients were severely ill. Most of the data concerns use of HCQ for treatment, but one study included used the medication as prophylaxis with excellent results. Many nations, including Turkey and India, are protecting medical workers and contacts of infected persons prophylactically. According to http://worldometers.info, deaths per million persons from COVID-19 as of Apr 27 are 167 in the U.S., 33 in Turkey, and 0.6 in India." [Emphasis added.]

26 Sarah Boseley, "Vital drug for people with lupus running out after unproven Covid-19 link," The Guardian, 27 March 2020, https://www.theguardian.com/world/2020/mar/27/vital-drug-people-lupus-coronavirus-covid-19-link-hydroxychloroquine

27 Jack Goodman and Christopher Giles, "Coronavirus and hydroxychloroquine: What do we know?" BBC News, 28 April 2020, https://www.bbc.co.uk/news/51980731

Alliance (Takeda and its collaborators) to develop a plasma-derived therapy.

28 Agence France-Presse, op. cit.

29 Tan Hui Yee, "Lupus patients hit by run on drug chloroquine after claims it wards against coronavirus," Strait Times, 25 March 2020, https://www.straitstimes.com/asia/se-asia/run-on-drug-chloroquine-despite-unproven-belief-as-ward-against-coronavirus-affecting

30 Camille Malplat, "Africans rush for chloroquine as virus tsunami looms" The Jakarta Post, 1 April 2020, https://www.thejakartapost.com/news/2020/04/01/africans-rush-for-chloroquine-as-virus-tsunami-looms-1585752420.html

31 Paul N Newton, Katherine C. Bond, et al., "COVID-19 and risks to the supply and quality of tests, drugs, and vaccines," The Lancet, 9 April 2020, https://doi.org/10.1016/S2214-109X(20)30136-4

The Global Therapeutics Picture: Fragmented, Uncoordinated and Mixed Results

The scale of the pandemic has set off a global race, not only for a vaccine, but also for therapeutics that can be clinically developed, trialled, approved quickly, and efficiently scaled and brought to market.

According to The Lancet there are 536 registered clinical trials (as of 24 April 2020) of which 332 are related to Covid-19. With respect to randomised clinical trials globally, results have been published on the following drugs:

- Lopinavir – ritonavir compared with standard of care
- Hydroxychloroquine compared with best supportive care
- Favipiravir compared with arbidol
- Lopinavir – ritonavir compared with arbidol[32]
- Remdesivir

The majority of the trials are located in countries most affected over the last two months: South Korea and China; rich countries in North America and Europe have upcoming trials while the rest of the Americas, Africa, southeast and south Asia, lag in terms of planned trials.[33] There are hundreds of additional Covid-19 clinical trials that are observational in nature and are not treated in this paper.[34]

Global Approach

(See Table 3 in the Annex for a table with data on clinical trials taking place globally.)

The WHO launched SOLIDARITY, a multi-national trial to test drugs approved for other uses. The mega-trial is designed to create a centralised database of trials and results that can be widely disseminated. The WHO is seeking to address the coordination gap through its multi-country clinical trials focused on therapeutics that could eventually enrol thousands of patients hospitalised with Covid-19. Guided by evidence derived from laboratory, animal and clinical studies, the SOLIDARITY trial is testing the efficacy of the following drugs:

- Remdesivir
- Lopinavir/Ritonavir
- Lopinavir/Ritonavir with Interferon beta-1a
- Chloroquine or hydroxychloroquine (the WHO has temporarily halted clinical trials of hydroxychloroquine)

Moreover, the trials will explore unapproved drugs that showed promise in animal studies to treat SARS and MERS. The WHO also has plans for using the same study design to test the drugs for their prophylactic use in frontline health care workers.

The WHO approach reduces the time taken to carry out randomised controlled trials by 80 per cent and enrols patients in one mega-trial that allows for comparative analysis of consistent data and results globally. Patients will know what drug is being administered, which could generate placebo effects; the studies are not double-blind. The WHO has to make a trade-off between rapid testing and results and scientific rigor. The design is not double-blind, which is the gold standard in medical research, so there could be placebo effects from patients knowing they received a candidate drug. As of 21 April 2020, hospitalised Covid-19 patients in more than 100 countries are participating in the trial, which is facilitated by donations made by various drug manufacturers.

There is another significant effort underway to support the rapid development of therapeutics, particularly in poor countries. The Covid-19 Therapeutics Accelerator was announced in early March and works with researchers, global regulators, the private sector, the WHO and governments. Its contributors are: Mastercard Impact Fund, which has committed up to $25 million; and Wellcome Trust and the Bill & Melinda Gates Foundation (BMGF), both of which have committed up to $50 million each. The BMGF has made a $100 million commitment to Covid-19 activities and its contribution to the Accelerator is part of that. The Accelerator is "designed to coordinate R&D efforts, remove barriers to drug development and scale up treatments to address the pandemic… [and] will share knowledge and resources across governments, the private sector, academia, and philanthropy… and welcome[es] new partners and collaborators…"[35] The accelerator provides "fast and flexible" funding that

32 Kristian Thorlund, et al., "A real-time dashboard of clinical trials for COVID-19," The Lancet, 24 April 2020, https://doi.org/10.1016/S2589-7500(20)30086-8

33 Comment, "Global coalition to accelerate Covid-19 clinical research in resource-limited settings," The Lancet, 2 April 2020, https://doi.org/10.1016/S0140-6736(20)30798-4

34 For the universe of Covid-19 trials that include: basic science; diagnostic tests; expanded access; interventional; observational; prevention; and prognosis, see "COVID-19 Trials Tracker," available at http://covid19.trialstracker.net/

supports "discovery and development to manufacturing," including scale up, with a commitment to ensuring that the most vulnerable can access and afford treatment. Implementation of Accelerator activities has already begun with two clinical trials that are testing whether chloroquine and hydroxychloroquine are effective in preventing people exposed to the virus from becoming ill. These trials do not duplicate WHO SOLIDARY trials, which explore whether chloroquine shortens length of symptoms in those suffering from Covid-19.[36]

High-Income Countries: Europe

The European Medicines Agency (EMA) listed the following treatments that are currently undergoing clinical trials to assess safety and efficacy: remdesivir; lopinavir/ritonavir; chloroquine and hydroxychloroquine; systemic interferons and, in particular, interferon beta (currently authorised to treat diseases such as multiple sclerosis); and monoclonal antibodies with activity against components of the immune system.[37]

The WHO trial has a European counterpart, called Discover, coordinated by French National Institute of Health and Medical Research (INSERM), which will test "standard of care, remdesivir, lopinavir and ritonavir in combination, the latter being administered with or without interferon beta and hydroxychloroquine."[38] The approach is flexible in that drugs that are shown to be ineffective can be quickly replaced by new ones. At least 800 French patients hospitalised with Covid-19 will be placed in the study, in addition to 3,200 patients from Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden and the UK.

A second initiative is underway, supported by €45 million in European Commission (EU) funding, provided to its research and innovations program, Horizon 2020. The money will be given to the Innovative Medicines Initiative (IMI), a partnership between the EU and the pharmaceutical industry (represented by European Federation of Pharmaceutical Industries and Associations (EFPIA), which is expected to provide an additional €45 million to the initiative.[39] Funding focuses on both diagnostics and therapeutics. In terms of the latter, two categories of therapeutics are the target:

"[D]evelopment of antivirals as well as other types of therapeutics to address a rapid response to the current Covid-19 outbreak;

35 https://www.therapeuticsaccelerator.org/

36 Angel Au-Yeung, "A Bill Gates-backed accelerator for Covid-19 therapeutics treatment partners with Madonna and Mark Zuckerberg's Chan-Zuckerberg initiative,"

Development of therapeutics to address the current and/or future coronavirus outbreaks"[40]

IMI leadership has consulted with other international research institutions to ensure that efforts are not duplicated and that there are no gaps in understanding the disease.[41] Research efforts in Europe are being supported by the European Medicines Agency, which provides drug developers with regulatory tools and ways to hasten product development.

High-Income Countries: The United States

In the US, drug companies and doctors have launched 144 trials involving remdesivir, chloroquine and hydroxychloroquine, Tocilizumab (TCZ) and lopinavir–ritonavir. In addition, the National Institutes of Health (NIH) – the largest biomedical research agency in the US – is trialling remdesivir at over 50 institutions; it also began a large trial for an anti-malarial drug.[42] The US arguably suffers more from lack of coordination than other regions of the world. The size of the US population, the weight of its powerful pharmaceutical industry and the still-formidable power of its government hold potentially grave implications for how therapies ae developed and distributed globally. A rational approach to generating efficacious therapeutics is hindered by duplication of trials and approaches (prevention vs. treatment; trials with and without control groups; drugs administered with and without other drugs/vitamins), too many small-N trials that will be unlikely to generate clear, actionable results; no criteria for prioritising what should be done; lack of clarity around which data should be collected and how they should be shared.[43]These failings are all the fruit of a lack of coordinated strategy, a roll uniquely suited to the federal government. An effort is under way to coordinate what is tantamount to a national strategy,

Forbes, 3 April 2020, https://www.forbes.com/sites/angelauyeung/2020/04/03/a-bill-gates-backed-accelerator-for-Covid-19-coronavirus-therapeutics-treatment-partners-with-madonna-and-mark-zuckerbergs-chan-zuckerberg-initiative

37 EMA press release, "Update on treatments and vaccines against COVID-19 under development," 31 March 2020, https://www.ema.europa.eu/en/documents/press-release/update-treatments-vaccines-against-Covid-19-under-development_en.pdf

38 INSERM press release, "Launch of a clinical trial against Covid-19," 22 March 2020, https://presse.inserm.fr/en/launch-of-a-european-clinical-trial-against-Covid-19/38737/

39 For more information, see "Covid-19: Horizon 2020 partly funding Innovative Medicines Initiative fast track call," 3 March 2020, https://ec.europa.eu/info/news/covid19-horizon-2020-partly-funding-innovative-medicines-initiative-fast-track-call-2020-mar-03_en

under the aegis of NIH. An announcement is imminent; the question is whether it will be captured by political interests in the same way that the testing issue has been. Private institutions are not sitting by idly awaiting a federal strategy but are undertaking their own steps to coordinate clinical trials. However valuable such efforts are, they are not a replacement for what federal government action can achieve.

High-Income Countries: Canada

The Canadian government already has a whole-of-government approach to address the coronavirus pandemic, including financial support for the development of therapeutics. To that end, it has announced two rounds of funding, the second of which has provided USD$ 194 million (Canadian $275 million) to "[e]nhance Canada's capacity in research and development, including research on medical countermeasures, including antivirals, vaccine development and support for clinical trials."[44] Seventeen proposals to study therapeutics received funding.[45] As of 27 May 2020, Health Canada has authorised 36 clinical trials for treatments.[46] In addition to featuring lopinavir/ritonavir, remdesivir, hydroxychloroquine and tocilizumab, trials are underway with: ribavirin (Virazole) to address respiratory distress; colchicine; nitric oxide (prevention and treatment of Covid-19); apheresis frozen plasma from recovered COVID-19 patients – convalescent plasma (to address acute Covid-19 respiratory illness); Vitamin C – ascorbic acid (to lessen organ dysfunction); and Kevzara – sarilumab (to address serious lung inflammation).

40 Innovative Medicines Initiative, "IMI2- Call 21," https://www.imi.europa.eu/apply-funding/open-calls/imi2-call-21

41 Florin Zubașcu, "Viewpoint: we need a coordinated global R&D response against the novel coronavirus," Science|Business, 10 March 2020, https://sciencebusiness.net/viewpoint/viewpoint-we-need-coordinated-global-rd-response-against-novel-coronavirus

42 Carolyn Y. Johnson, "Chaotic search for coronavirus treatments undermine efforts, experts say," Washington Post, 15 April 2020, https://www.washingtonpost.com/health/2020/04/15/coronavirus-treatment-cure-research-problems/

43 Ibid.

44 CA government press release, "Prime Minister outlines Canada's Covid-19 response," 11 March 2020, https://pm.gc.ca/en/news/news-releases/2020/03/11/prime-minister-outlines-canadas-Covid-19-response

45 Canadian Institutes of Health Research, "Canadian 2019 Novel Coronavirus (Covid-19) Rapid research Funding Opportunity Results," 19 March 2020, https://cihr-irsc.gc.ca/e/51908.html

46 For a detailed list, see "Vaccines and treatments for Covid-19: List of all Covid-19 Clinical Trials Authorised by Health Canada," https://www.canada.ca/en/health-canada/

High-Income Countries: South Korea

The government's Ministry of Food and Drug Safety is taking the same approach that other countries are: testing existing drugs approved for other purposes. To that end, it has authorised clinical trials for remdesivir and hydroxychloroquine. The Korean government has also approved use of six influenza treatments for coronavirus care.

Low and Middle-Income Countries: Africa

Clinical trials are foundational to evidence-based medicine and the resulting development of drugs. Resources and infrastructure for clinical trials do exist in Sub-Saharan Africa but they are concentrated in countries that have prioritised such investments, such as South Africa. The dearth of clinical trials taking place in Sub-Saharan Africa is cause for grave concern for political leaders, public health officials and international institutions involved in responding to Covid-19. Any drugs eventually approved for therapeutics may be of limited utility in Africa because of a lack of testing on genetically diverse populations. A scientific study from 2009 found that Africa contains the world's most diverse DNA.[47] Excluding such diversity means that trial results will not be generalisable to large populations; it also means that any treatments developed will not be tailored to the various African groups, which should not be treated as homogenous because responses to drugs are influenced by genetics.[48] Moreover, other local factors such as administering drugs in rural areas or how antiretrovirals could affect people living with HIV underscore the need for localised trials.

A review of the NIH master list of clinical trials for treating Covid-19 shows that Africa hosts very few: 19 are in Egypt; three are in Tunisia; and Sub-Saharan Africa hosts a total of three despite its population of more than 1 billion people. South Africa and Zambia are both participating in a Phase 3 "randomized, multi-center, transdisciplinary, international placebo-controlled trial," that is sponsored by Washington University School of Medicine, which is based in St. Louis, Missouri in the US, with support from the BMGF, with health-care workers as the participants.[49] The objective is to prevent health care systems from collapsing under the weight of Covid-19 admissions. Chloroquine and hydroxychloroquine are being

services/drugs-health-products/covid19-clinical-trials/list-authorized-trials.html#wb-auto-5

tested, with results expected in February 2021 for South Africa and April 2021 for Zambia. As of now, the WHO SOLIDARITY trial has generated the most engagement with African countries. Kenya, Nigeria, and South Africa have joined the SOLIDARITY trial, with Burkina Faso and Senegal in the process of registering and 25 others expressing interest.[50] Wider African participation is hindered by regulatory hurdles as the drugs must be cleared for import and then inspected for safety and ethics, and there are also challenges with staffing and supplies.[51] Support for dealing with regulatory approvals has been offered by the Covid-19 Research Coalition.

A new multinational, randomised, open-label, factorial trial is opening in Nigeria, sponsored by London School of Hygiene and Tropical Medicine. It will test aspirin, Losartan (which is used to treat high blood pressure) and Simvastatin (which is used to lower cholesterol) on 10,000 patients hospitalised with Covid-19.[52] All three drugs are on the WHO's list of essential medicines, are affordable and widely available in Africa and are easily administered. Finally, if any readily available drug is approved, then productive capacity and scaling up will be less challenging because all three are available in generic form and are manufactured in many factories around the world.[53] The LSHTM trial of particular interest because it highlights drugs that less commonly tested. Moreover, it is implementing an infrastructure that could accommodate trials of other drugs.

Lack of Global Coordination Affects the Development of Therapeutics, Especially in Poorer Countries

A global coalition of scientists, doctors, funders and public policymakers has issued a call for attention to and coordination of efforts to develop therapeutics for use in resource-poor settings. The COVID-19 Clinical

47 Joel Achenbach, "Study finds Africans more genetically diverse than other populations," Washington Post, 1 May 2009, https://www.washingtonpost.com/wp-dyn/content/article/2009/04/30/AR2009043002485.html

48 Ibid. See also Clint Witchalls, "Few clinical trials are done in Africa: Covid-19 shows why this urgently needs to change," The Conversation, 6 April 2020, https://theconversation.com/few-clinical-trials-are-done-in-africa-Covid-19-shows-why-this-urgently-needs-to-change-135117

49 US National Library of Medicine, https://clinicaltrials.gov/ct2/show/NCT04333732?cond=COVID-19&map_cntry=ZA&draw=2&rank=1 More specifically, "[h]ealthcare worker based in a primary, secondary or tertiary healthcare setting with a high risk of developing Covid-19 due to their potential exposure to patients with SARS-CoV-2 infection."

Research Coalition – which focuses its coordination efforts on low and middle-income countries – argues that

"Priority should be given to interventions that reflect the specific needs of countries and are readily implementable. For resource-poor settings, that means interventions need to be affordable and available, and adaptable to the health-care systems and the populations they serve. The adverse impacts of COVID-19 on health and welfare are likely to be considerable in low-income or middle-income countries (LMICs). Clinical trials, and evaluations of affordable and implementable interventions of all types—behavioural, organisational, medical, and supportive—are a priority…"

Large, well conducted clinical trials are needed urgently to support guidelines on prevention and clinical management. These trials must not detract from already overstretched health services and, with travel bans in many places, they must be designed to accommodate remote initiation and monitoring. There is also much that might be improved in supportive care and organisation in LMIC settings that could reduce direct and indirect Covid-19 morbidity and mortality. Research is needed now to guide the increasingly difficult choices that resource-limited health-care systems will face. Yet additional challenges that relate to ethics review, regulation, manufacturing, clinical trial support and logistics, open science and data sharing, and equitable and affordable access will need to be overcome for these studies to be successful."[54]

Their call is timely and necessary and requires the imprimatur of political leaders.

Scientists and public health experts have raised additional concerns about the nature of the ongoing clinical trials themselves. Many are related to the lack of global coordination, which risks making the results of the trials and studies less useful for securing fast approval of therapies. First, many studies conflict and generate inconclusive results, often because of small sample sizes. It is not uncommon for trials that look promising with small Ns (sample sizes) to face failure with more rigorous large-N trials. Some public health experts argue a different point: that the issue is less the sample size and more the nature of how the trials are designed. For example, small-N

50 Antoaneta Roussi and Amy Maxmen, "African nations mission from coronavirus trials," Nature, 3 April 2020, https://www.nature.com/articles/d41586-020-01010-7

51 Ibid.

52 US National Library of Medicine, https://clinicaltrials.gov/ct2/show/NCT04343001?cond=COVID-19&map_cntry=NG&draw=2&rank=1#contacts

53 Interview with Professor Haleema Shakur-Still and Professor Ian Roberts, co-leads of the clinical trial in Nigeria and Pakistan, and on faculty at London School of Hygiene & Tropical Medicine.

trials can yield clear results if they are well-designed; this could be achieved by targeting a very specific group. Such a trial, for example, would not enrol both patients hospitalised with severe Covid-19 symptoms in the ICU and those who are only mildly symptomatic and are not hospitalised. Small-N trials are effective in fields such as oncology, particularly with rare cancers. Second, different trials testing the same drugs often have different methodologies (some may be double-blind, others not, for example), which makes consistency of analysis across them difficult. Such results make it difficult to generate and share consistent data that can be usefully shared so as to identify additional questions or clues for how to develop answers to key research questions. Third, it is also unclear from piecemeal studies how to combine the knowledge that exists among different researchers so as to better prioritise what should be studied and how. Fourth, the universe of patients available for participation in clinical trials is finite, despite the large number of people infected and hospitalised. Clinical trials often seek to recruit the same patients, revealing underlying challenges with recruitment, tracking and bureaucracy. Finally, it is not clear what the next steps will be with respect to taking promising and credible results and turning them into actual therapeutics. The scale of the pandemic and the differing positions of countries affected by the novel coronavirus raises the spectre of inequality. For example, only some countries have access to the foundational components, such as APIs, necessary to mass-produce therapeutics.

A lack of coordination is distorting the market for potentially life-saving drugs and political leaders have not embraced a coherent policy response. Pharmaceutical companies play a critical role and are treated in the next section.

54 Covid-19 Clinical Research Coalition, "Comment: Global Coalition to accelerate COVID-19 clinical research in resource-limited settings," The Lancet, 2 April 2020, https://doi.org/10.1016/S0140-6736(20)30798-4

Therapeutics, Pharma, Pricing and Accessibility: The Return of Compulsory Licensing or New Forms of Global Coordination?

The scale of the pandemic necessitates that any drugs that are eventually approved for treatment be manufactured at scale for a global population that stands at 7.8 billion people. Pharmaceutical companies working on therapeutics have been inconsistent with messaging around the pricing of drugs. They are under immense pressure to modify their current pricing methodology and other marketing strategies in order to ensure access – especially for poor countries. Pharma pricing is not controlled only by companies but is heavily regulated, reviewed and negotiated with payers and other bodies. Early statements released by a few executives participating in a virtual press briefing held by the international pharmaceuticals trade association (IFPMA) seemed to suggest that companies were considering affordability and access. However, subsequent statements that appeared in the IFPMA's manifesto were silent on these issues.[55] Predicting how pharmaceutical companies will react to the current crisis is difficult given the diversity of characteristics within the industry: companies differ in terms of their size, types of investors, the competitive landscape, and possible products and capacity. All these factors contribute to how pricing and accessibility are determined.[56] It is unsurprising that, given the potential for significant returns to investors is very high, several investment banks are encouraging drug companies to increase prices on new drugs that make it to market.

Access to what could potentially be life-saving drugs will hinge not only on price and the production capacity of drug manufacturers, but also on government action. Many countries are reliant on imported drugs. In the case of the UK, 80 to 90 per cent of its drugs come from abroad. APIs are the backbone of the drug supply chain and these basic molecules are manufactured in China, which then exports them to countries that turn them into injections and tablets. India leads the world in generic drug production and manufactures 25 per cent of all drugs administered in the UK; China is also a top-five provider of drugs for the UK outside the EU.[57] As a result, drug production in and exports from India have declined, with the government temporarily prioritising domestic use. If any of the drugs currently being trialled are eventually approved for treatment, scarcity could ensue as some of them have low production costs and are small molecules, which could easily set off intense global competition for limited supplies.[58] The impact of the pandemic on China along with concerns

about breaches of facilities in China and India affecting APIs have sparked discussions in various countries about reshoring production of critical medicines. The cost to do so will likely be higher than what countries pay for production and manufacturing in China and India, but Covid-19 has raised the issue to the level of national security.

Some governments are acting to ensure access and affordability; several are either granting compulsory licenses or are putting in place steps that will allow such licenses to be granted either faster or with greater ease. (See Table 4.) On 20 March 2020, Ecuador's National Assembly unanimously voted to allow the government to issue compulsory licenses for Covid-19 related drugs. On the same day AbbVie, which holds the patent for Kaletra (lopinavir/ritonavir), effectively lifted its patent to allow for the drug to be manufactured generically to treat Covid-19. Similarly, Gilead and five generic pharmaceutical companies in Pakistan and India are partnering to increase stocks of remdesivir in 127 low- and middle-income countries (LMICs). The deals are royalty-free, non-exclusive and allow the companies to set their own prices for generic versions of remdesivir.[59] Novartis has pledged to make available the IP on its repurposed hydroxychloroquine. Finally, a number of vaccine makers are making similar pledges but this has not prevented a wide swath of European parliamentarians from publicly stating their support for compulsory licensing to ensure access to any eventual Covid-19 vaccine.

As countries face increased numbers of cases, drug companies surely will be confronted with desperate governments seeking easier, more affordable access to any therapeutics that make it to market. For the US and the EU, the picture with respect to compulsory licensing is somewhat more complicated, due to their regulatory agencies (the FDA and the EMA, respectively), which have granted regulatory exclusivities for data (preventing the use of clinical data for several years) and market protection.[60] It is too soon to know how many clinical trials will lead to approved treatment drugs, or if drug makers will insist that governments comply with such exemptions. Negotiations may obviate the need for

55 Yannis Natsis, "Will pharma commit to delivering affordable therapeutics against COVID-19?" European Public Health Alliance, 6 April 2020, https://epha.org/will-pharma-commit-to-delivering-affordable-therapeutics-against-Covid-19/

56 Ibid.

57 Emma Wilkinson, "India and China spark concerns for UK drug supplies," The Pharmaceutical Journal, 28 August, 2019, https://www.pharmaceutical-journal.com/news-and-analysis/features/india-and-china-spark-concerns-for-uk-drug-supplies/20206998.article

58 Andrew Hill, "Ways to safeguard UK drug supplies during Covid-19 and beyond," The Pharmaceutical Journal, 15 April 2020, https://www.pharmaceutical-journal.com/news-and-analysis/opinion/comment/ways-to-safeguard-uk-drug-supplies-during-covid-19-and-beyond/20207897.article

contentious interactions.[61] Ultimately, compulsory licensing is not the most effective tool for the future of research and investment from companies – collaboration rather than compulsion is key.

In response to concerns about individual government action on licensing challenges, Costa Rica's leaders have presented a proposal to the WHO. In the proposal, President Carlos Alvarado and Health Minister Daniel Salas suggest "creating a repository of information on diagnostic tests, devices, medication or vaccines, with free access or licensing on reasonable and affordable terms, in all member countries of the WHO." The proposal "further urges the WHO to develop a memorandum of understanding to share this technology, and to promote its implementation with financial support from the public and private sectors, as well as from international organizations."[62]

There are several merits to such a voluntary agreement, which seeks to pool critical resources such as technologies, knowledge, and data in order to prevent, detect and treat Covid-19. The proposal recognises the need to increase the likelihood that Covid-19-related outputs will be less expensive and therefore more accessible, especially for poor countries. It also includes the value chain: "patents on inventions and designs, regulatory test data, research data including outcomes, know-how, cell lines, copyrights and blueprints for manufacturing, as these rights relate to equipment, diagnostic tests, devices, medicines, vaccines and other medical tools."[63] Along with the Costa Rican President's proposal, WHO-hosted Unitaid also sent a proposal. "In close coordination with WHO and other partners, [UNITAID] plan[s] to fund specific actions to enhance access to tests and to potential new medicines and technologies."[64] A wide range of relevant actors – from pharmaceutical companies and medical device companies, to research institutions – could participate with ongoing contributions to build a wider and deeper library of content. It was boosted by UK support, along with the Medicine Patent Pool expanding its mandate to cover Covid-19 products. It remains to be seen whether pharmaceutical companies will actively support the initiative.

---

59 "Global calls for compulsory Covid-19 patent licensing build," I Am Media, 21 May 2020, https://www.iam-media.com/coronavirus/global-calls-compulsory-covid-19-patent-licensing-build

60 "Covid-19 emergency may expose compulsory licensing limits," IAM – Media, 24 March 2020, https://www.iam-media.com/coronavirus/Covid-19-emergency-may-expose-compulsory-licensing-limits

61 Ibid.

62 CR government press release, "Costa Rica submits proposal for WHO to facilitate access to technologies to combat Covid-19," 24 March 2020, https://www.presidencia.go.cr/comunicados/2020/03/costa-rica-submits-proposal-for-who-to-facilitate-access-to-technologies-to-combat-Covid-19/ and cited in Achal

Prabhala and Ellen't Hoen, "We'll find a treatment for coronavirus – but drug companies will decide who gets it," The Guardian, 15 April 2020, https://www.theguardian.com/commentisfree/2020/apr/15/coronavirus-treatment-drug-companies

63 Brook Baker, "Rationale for supporting Costa Rica's proposal for emergency Covid-19 technology IP pool for all countries," Health Gap, 25 March 2020, https://healthgap.org/rationale-for-supporting-costa-ricas-proposal-for-emergency-covid-19-technology-ip-pool-for-all-countries/

64 Letter from Marisol Touraine (Chair, Unitaid Executive Board) and Dr Philippe Duneton (Executive Director, a.i Unitaid) to Dr. Tedros (Director General, WHO), 25 March 2020, https://www.healthpolicy-watch.org/wp-content/uploads/2020/03/unitaid.pdf

Conclusion

The Covid-19 pandemic has generated a flurry of activity to find viable treatments. Any drugs that are eventually approved would constitute a key part of helping governments re-open their economies, ease pressure on health care systems and restore health to their populations. Better coordination among political leaders will help address the various challenges that currently exist and make it more likely that safe treatment will be available for all who need it.

Annex

Table 1 – Trials underway for potential Covid-19 treatments

This information is taken from the website of the National Institute for Health Research's urgent public-health Covid-19 studies
(data current as of 26 May 2020)

Study name and drug(s) to be analysed	Manufacturer/ funder/ sponsor	Clinical trial	Approval date	Study description
5773 Safety and Antiviral Activity of Remdesivir for severe Covid-19 Remdesivir	Gilead Sciences	Phase 3 randomised study	25 March 2020	"Evaluate the efficacy of 2 remdesivir (RDV) regimens with respect to the normalization of temperature and oxygen saturation through Day 14 in participants with severe coronavirus disease (Covid-19)"
5774 Safety & ~~Antiviral Activity of Remdesivir for moderate Covid-19 Remdesivir~~	Gilead Sciences	Phase 3 randomised study	25 March 2020	Evaluate the drug's efficacy in time to discharge in patients with moderate Covid-19 patients
A study to evaluate ~~TCZ in patients with severe Covid-19 Pneumonia Tocilizumab~~ (TCZ)	F. Hoffmann-La Roche Ltd	Randomised, double-blind, placebo-controlled, multi-centre study	26 March 2020	Patients with severe Covid-19 pneumonia
ACCORD, multiple candidate agents	Sponsored by University Hospital Southampton NHS Foundation Trust, funded by NIHR/ UKRI	Multicentre, seamless, Phase 2 Adaptive Randomisation Platform study	21 April 2020	Hospitalised Covid-19 patients

Study name and drug(s) to be analysed	Manufacturer/ funder/ sponsor	Clinical trial	Approval date	Study description
Adaptive Covid-19 Treatment Trial (ACTT) Remdesivir	Sponsored by University of Minnesota (USA), with funding from National Institutes of Health (NIH), United States	Multicentre, adaptive, randomised blinded, controlled trial controlled trial	27 March 2020	For Covid-19 treatment in hospitalised adults
CANCOVID Canakinumab (CANCOVID)	Novartis	Phase 3 multi-centre, randomised, double-blind, placebo-controlled study	6 April 2020	Covid-19 pneumonia and cytokine release syndrome
CATALYST	Funder N/A, sponsor University of Birmingham		11 May 2020	Randomised phase II proof of principle multi-arm multi-stage trial designed to guide the selection of interventions for phase III trials in hospitalised patients with COVID-19 infection
COG-UK HOCI	Sponsored by University College London, funded by NIHR/UKRI	N/A	11 May 2020	COG-UK Hospital Onset COVID-19 Infection Study
CROWN CORONATION (hydroxy)chloroquine	Funded by Bill & Melinda Gates Foundation; Washington University in St Louis (USA)	University College London	13 May 2020	An international, multi-site, Bayesian platform adaptive, randomised, double-blind, placebo-controlled trial assessing the effectiveness of varied doses of oral Chloroquine
Chloroquine prevention of coronavirus disease (Covid-19) in the healthcare setting	Sponsored by University of Oxford, funded by Wellcome	Randomised, placebo-controlled, prophylaxis study	30 March 2020	prevention and in the treatment of Covid-19 infections in frontline health workers and other

Study name and drug(s) to be analysed	Manufacturer/ funder/ sponsor	Clinical trial	Approval date	Study description
(COPCOV) Chloroquine (Asia) and hydroxychloroquine (Europe)	Trust			frontline staff
ILIAD 7 Recombinant InterLeukin-7 (CYT107)	Sponsored and funded by RevImmune	Phase II randomised clinical trial is in the process of regulatory submission	6 April 2020	"prevent patients who are in the hospital for Covid-19 from progressing to having to be treated in the ICU"
PRINCIPLE Hydroxychloroquine or the antibiotic Azithromycin	University of Oxford sponsored, UKRI / NIHR funded	1st clinical trial Platform Randomised trial of Interventions against Covid-19 In older people	11 March 2020	reduce the need for people to go to hospital or speed up their recovery for older people (over 50 with comorbidities and over 65 years old
RECOVERY TRIAL Lopinavir-Ritonavir, Interferon β1b, low-dose corticosteroids, hydroxychloroquine	Sponsored by University of Oxford, funded by Medical Research Council	Randomised evaluation	11 March 2020	"As well as normal hospital treatment patients with Covid-19 infection will either receive no additional experimental treatment, or will receive one of the following treatments: - a combination of Lopinavir-Ritonavir (antiviral drugs) - interferon β1b (used to treat some kinds of multiple sclerosis) - low-dose corticosteroids (used to reduce inflammation) - hydroxychloroquine (similar to a drug used to treat malaria)"
REMAP – CAP "anti-viral drugs (Lopinavir-Ritonavir and hydroxychloroquine),	Sponsored by University Medical Centre Utrecht	Randomised, embedded, multifactorial, adaptive platform trial	27 March 2020	"generate evidence that can be applied during the pandemic to reduce mortality, reduce

Study name and drug(s) to be analysed	Manufacturer/ funder/ sponsor	Clinical trial	Approval date	Study description
steroids to reduce inflammation and treatments which act on the immune system, often used to treat other conditions such as rheumatoid arthritis, (interferon-ß1a, anakinra, tocilizumab and sarilumab" + more treatments as new evidence emerges	(Netherlands), funded by the European Commission	for community-acquired pneumonia		intensive care use, and reduce morbidity in severely ill patients with Covid-19 infection"
Repair of ARDS by Stromal Cell Administration (REALIST) Mesenchymal Stromal Cells (MSCs)	Sponsored by Belfast Health & Social Care Trust, funded by Wellcome Trust	Phase 1 trial followed by a randomised, double-blind, placebo-controlled phase 2 trial.	02 April 2020	"A trial of Mesenchymal stromal Cells (MSCs) for acute respiratory failure"
RUXCOVID Ruxolitinib	Sponsored and funded by Novartis	Phase 3 randomised, double-blind, placebo-controlled multi-centre study	6 April 2020	assess the efficacy and safety of ruxolitinib on Cytokine Release Syndrome (CRS) in patients with Covid-19
SARS-CoV-2 Infection inhaled SNG001 (IFN-β1a – interferon beta -- for nebulisation)	Sponsored and funded by Synairgen Research Limited	randomised double-blind placebo-controlled trial	30 March 2020	prevent/limit the worsening of lower respiratory tract illness
STOP-COVID 19 Brensocatib (INS1007)	Sponsored by University of Dundee, funded by Insmed, Inc.	Randomised, double-blind, placebo-controlled trial	21 April 2020	" evaluate the potential of Brensocatib (INS1007) as a novel host directed therapy for the treatment of adult patients hospitalized with Covid-19"

Study name and drug(s) to be analysed	Manufacturer/ funder/ sponsor	Clinical trial	Approval date	Study description
nCOV: Developing CoV-bnMABs for therapy of highly pathogenic coronaviruses including SARS-CoV-2 developing antibodies	Funded by UKRI/NIHR, sponsor N/A, CI is Professor Xiao-Ning Xu	Pre-clinical	11 March 2020	Develop potential antibody therapy
Repurposing FDA-Approved Drugs for Treatment of 2019-nCoV-induced Disease "library of approximately 1,000 drugs already approved for use in humans"	Sponsored by Queens University Belfast, funded by, UKRI / NIHR	Pre-clinical	11 March 2020	Tests on cells in the laboratory to determine if any can reduce the toxic effects of novel coronavirus infection

Table 2 – Sermo's global survey of 5,000 physicians globally

Overall Perceived Efficacy of All Treatments by Setting

(Efficacy: % of physicians who rate the drug very or extremely effective; chart reflects all treaters who have used drug in respective setting)

Share of physicians rating drug very/extremely effective within setting (base size)	Non-hospital	Hospital	ICU	Overall
Plasma	68% (34)	61% (103)	53% (73)	57%
Tocilizumab	41% (34)	52% (189)	27% (128)	44%

High-dose Steroids	46% (83)	44% (289)	36% (162)	42%
Remdesivir	27% (37)	34% (146)	30% (98)	31%
Hydroxychloroquine	38% (231)	31% (632)	24% (300)	30%
Vitamin D	27% (90)	21% (121)	27% (49)	24%
Bronchodilators	26% (247)	25% (418)	26% (200)	24%
Anti-HIV drugs	27% (70)	22% (323)	26% (156)	23%
Vitamin C	26% (150)	19% (192)	18% (98)	22%
Zinc	25% (80)	20% (93)	14% (57)	22%
Drugs to treat flu	24% (128)	26% (253)	28% (102)	22%
Azithromycin	23% (342)	19% (662)	21% (271)	20%

65

Table 3 – Clinical trials by region

Source: https://clinicaltrials.gov/ct2/results/map?cond=COVID-19&map=
(data current as of 26 May 2020)

Region	**Country**	**Number of clinical trials (1673 in total)**
North America	United States	340

Region	Country	Number of clinical trials (1673 in total)
	Canada	48
	Mexico	19
Central and South America	Argentina	10
	Bolivia	1
	Brazil	23
	Colombia	11
	Costa Rica	1
	Chile	4
	Ecuador	2
	French Guiana	3
	Guatemala	1
	Peru	1
	Uruguay	1
	Venezuela	1
Western Europe	Belgium	31
	France	267
	Germany	52
	The Netherlands	15
	Iceland	2

65 https://www.sermo.com/press-releases/sermo-reports-jury-is-still-out-on-remdesivir-31-of-physicians-who-have-used-remdesivir-rate-it-as-highly-effective-31-rate-it-with-low-effectiveness-38-rate-it-as-somewhere-in-the-middle/

Region	Country	Number of clinical trials (1673 in total)
	Republic of Ireland	5
	Luxembourg	1
	Switzerland	29
	United Kingdom	65
Central and Eastern Europe	Albania	1
	Austria	14
	Belarus	1
	Bosnia and Herzegovina	1
	Croatia	2
	Estonia	1
	Hungary	6
	Lithuania	1
	Poland	14
	Romania	6
	Russia	12
	Slovakia	1
	Slovenia	3
	Ukraine	1
Southern Europe	Cyprus	2

Region	Country	Number of clinical trials (1673 in total)
	Greece	11
	Italy	96
	Portugal	7
	Spain	79
Northern Europe	Denmark	30
	Finland	1
	Norway	14
	Sweden	17
Middle East/North Africa	Egypt	42
	Iran	18
	Iraq	1
	Israel	17
	Jordan	4
	Lebanon	3
	Kingdom of Saudi Arabia	9
	Tunisia	7
	Turkey	33
South Asia	India	12
	Pakistan	8

Region	Country	Number of clinical trials (1673 in total)
Sub-Saharan Africa	Nigeria	2
	Senegal	1
	South Africa	3
	Sudan	1
	Zambia	1
East Asia/Pacific	Australia	11
	China	103
	Hong Kong	14
	South Korea	7
	Taiwan	6

Table 4 – Government action on compulsory licensing

(data current as of 26 May 2020)

Country	Action taken	Date
Chile (unanimous vote in lower chamber)	"[A]dopted a resolution declaring that the global coronavirus outbreak justifies the use of compulsory licensing to facilitate access to vaccines, drugs, diagnostics, devices, supplies, and other technologies useful for the surveillance, prevention, detection, diagnosis and treatment of people infected by the coronavirus virus in Chile." [66]	17 March 2020
Israel	Issued compulsory patent licenses for lopinavir/ritonavir (brand name Kaletra). The	19 March 2020

66 Ellen't Hoen, "Covid-19 and the comeback of compulsory licensing," Medicine, Law,

Country	Action taken	Date
	attorney general invoked a 1967 patent law. The drug will be manufactured in India.	
Ecuador	The National Assembly's Education, Culture, Science and Technology Commission approved a resolution for the Minister of Health to give compulsory licenses for Covid-19-related technologies.[67]	20 March 2020
France	"[A]rticle allows the Prime Minister, when a state of health emergency is declared, and for the sole purpose of guaranteeing public health: • to order the requisition of all goods and services necessary to fight the health disaster and of any person necessary for the operation of these services or the use of these goods • to take **all measures to make available to patients** appropriate **medicines for the** eradication of the health disaster;"[68]	23 March 2020
Canada	"The Covid-19 Emergency Response Act grants the Commissioner of Patents the power to authorise use of a patented invention to the extent necessary to respond to a public health emergency. This form of compulsory licensing builds on the existing framework that has allowed government use of a patented invention."[69] (hastening the process)	25 March 2020
Germany	Act on the Protection of the Population in Case of an Epidemic Situation of National Significance provides for patented technologies to be used to make, offer and market (hastening the process).	27 March 2020

and Policy, 23 March 2020, https://medicineslawandpolicy.org/2020/03/Covid-19-and-the-come-back-of-compulsory-licensing/. The English translation of the resolution is available at https://www.keionline.org/chilean-covid-resolution. The key text is, "the coronavirus epidemic worldwide and in our country, and its risks to the health of the Chilean population, in accordance with the aforementioned, constitute sufficient justification for the granting of the non-voluntary licenses contemplated in article 51º No. 2 of Industrial Property Law No. 19.039 to facilitate access to vaccines, drugs, diagnostics, devices, supplies, and other technologies useful for the surveillance, prevention, detection, diagnosis and treatment of people infected by the coronavirus virus in Chile, for public health reasons and/or national emergency, as provided in international laws, particularly the Doha Declaration on the TRIPS Agreement and Public Health."

67 The English text of the resolution is available at https://www.keionline.org/ecuador-CL-coronavirus-resolution: "Demand the President of the Republic and the Minister of Public Health of Ecuador, that within the declaration of a State of Health Emergency,

Country	Action taken	Date
Brazil	Proposed bill for compulsory licensing for Covid-19 related medicines and vaccines.[70]	Proposed 13 April 2020

include the administrative and technical mechanisms for the establishment of compulsory patent licenses, access to test data and access to other technologies for the availability of vaccines, drugs, diagnoses, devices, supplies, and other useful means for the surveillance, prevention, detection, diagnosis, and treatment of people infected with the Coronavirus (COVID-19) and other variations in order to guarantee the right to health through its free access or at an affordable costs. Article 2.- Require the Minister of Public Health of Ecuador that within the declaration of State of Health Emergency also provide for non-commercial public use or the compulsory license of patents, as well as access to test data for pharmaceutical products for the production, import or massive use in Ecuador of vaccines, drugs, diagnoses, devices, supplies, and other useful technologies for the surveillance, prevention, detection, diagnosis, and treatment of people infected with the Coronavirus (COVID-19) and others variations, in coordination with the competent technical organizations."

68 Francois Pochart, "Compulsory licenses granted by public authorities: an application in the Covid-19 in France?" Kluwer Patent Blog, 23 April 2020, available online at http://patentblog.kluweriplaw.com/2020/04/23/compulsory-licenses-granted-by-public-authorities-an-application-in-the-covid-19-crisis-in-france-part-1/?doing_wp_cron=1590504122.8295719623565673828125

69 "Compulsory licensing in Canada – revisited," Life Sciences Intellectual Property Review, 21 April 2020, available online at https://www.lifesciencesipreview.com/article/compulsory-licensing-in-canada-revisited

70 See https://www.statnews.com/wp-content/uploads/2020/04/brazil-cl-proposal-1.pdf for the proposed bill. One relevant passage is "The declaration of public health emergency of international concern by the World Health Organization (WHO) or the declaration of public health emergency of national concern by the competent national authorities automatically warrants the granting of compulsory license for national emergency of all patent applications or patents in force relating to technologies used to address the respective health emergency, such as vaccines, medicines, diagnostic tests, reagents, medical devices, personal protective equipment, supplies and any other technologies used to meet health needs related to the emergency."

FOLLOW US
facebook.com/instituteglobal
twitter.com/instituteGC
instagram.com/institutegc

GENERAL ENQUIRIES
info@institute.global

FIND OUT MORE
INSTITUTE.GLOBAL