TONY BLAIR INSTITUTE FOR GLOBAL CHANGE

Therapeutics and Politics: The Evolving Covid-19 Treatment Landscape

EVA THORNE

Contents

How the Therapeutics Landscape Is Evolving *4*
The Need for Coordinated Drug Discovery and Distribution *5*
Ensuring Equitable Access to Treatment *8*
Annex *10*

Published at https://institute.global/policy/therapeutics-and-politics-evolving-covid-19-treatment-landscape
on August 21 2020

We are now experiencing our new reality – one where the entire world will be living with Covid-19 for the foreseeable future. While recent announcements from pharmaceutical companies such as AstraZeneca provide cautious optimism that a successful vaccine will emerge, the path from here to global distribution is fraught, particularly for developing countries that lack the purchasing power of wealthier nations – which are already are buying doses in large quantities.

Aside from the logistical challenges, which range from ramping up manufacturing to ensuring critical supplies such as needles and syringes are available, there is the thorny – and political – issue of who will receive the vaccine first. Although there has been some progress through global facilities such as COVAX – which seeks to procure 2 billion doses by the end of 2021 that will vaccinate 20 per cent of participating countries' populations – most poorer countries are still battling for vaccine access. [1]

How the Therapeutics Landscape Is Evolving

Events since the publication of our Therapeutics and Covid-19 paper in May provide additional confirmation of one of its central arguments: Successful treatment of Covid-19 is as important as ever to the containment of the disease. 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. These are critical for economic recovery to occur. Moreover, there is some evidence derived from early clinical trials that if administered early during the infection, some treatments may halt the progression of the disease. Robust, late stage clinical trials will be necessary to establish this. If proved true, this would most certainly be a game-changer and provide a bridge to vaccines, if not a complement. Given the fact that many treatments in clinical development are off-label drugs, it is likely that an effective treatment will be available to the general public before a vaccine.

Over the past few months, the therapeutics landscape has undergone significant change, as some drugs that were in widespread use have been scientifically proven to be ineffective and even harmful. The much-vaunted hydroxychloroquine, despite continued showcasing by political leaders in the US and Brazil, has been removed from the World Health Organisation's Solidarity Trial. In June, the UK megatrial, Recovery, showed definitively that the combination of lopinavir and ritonavir, two antiretrovals known to fight HIV, were ineffective as Covid-19 treatments. It also delivered clear findings that dexamethasone, an inexpensive steroid, reduced deaths by one-third in ventilated patients. For patients on oxygen, mortality declined by about one-fifth. Dexamethasone, which can be administered both orally and intravenously, has now been approved in the UK for all patients who require oxygen, including those on ventilators; Japan has also approved its use. Avigan (favilavir) has been approved in China, Italy and Russia. Meanwhile, the antiviral remdesivir has become the first drug to be approved to treat Covid-19 in Europe, Japan, and Australia. Marketed under the brand name Velkury, it must be administered intravenously. Less positive is the cost of a five-day treatment: $2,340 in Europe and $3,120 in the US, where remdesivir has emergency use authorization from the Food and Drug Administration.

In June, US President Donald Trump took the step of purchasing the entire global supply of the drug, coming under criticism. That action alone underscores how pharmaceutical nationalism is likely to remain a feature of the Covid-19 landscape, given the political context of declining multilateralism, the rise of autocratic populists. Rich countries will continue to engage in bilateral or bloc-wide negotiations (in the case of the EU) with drug companies to secure domestic supply, while philanthropic initiatives will press to ensure global access and equity. The political (and evidence-based) argument that must be embraced by politicians in rich countries is that the Covid-19 pandemic knows no borders; its existence *anywhere* in the world is a threat to *every country*. The best investment is one that provides vaccines and treatments to *all who need it*; rich countries have the means, even with the recessions that they face, to ensure global coverage. This can be achieved through bulk purchasing, which could also help reduce the cost of vaccines. Or countries such as Japan, Brazil and others that have spare manufacturing capacity could meet the needs of poorer countries.

The Need for Coordinated Drug Discovery and Distribution

Therapeutics to treat Covid-19 fall into two categories: new and off-label. New treatments in clinical development include convalescent plasma; hyperimmune plasma; LY-CoV555, a human antibody; and natural killer (NK) cells, the major cells of the natural immune system. However, the overwhelming majority of drugs fall into the latter category and hold the promise of reaching the market faster than new ones. Many off-label drugs are available as generics, which increases the likelihood that they can be manufactured at scale, at pace and made available to poor countries in particular.

It is worth highlighting one particular type of drug that could be a game-changer. The deepening fund of knowledge developed through trialling various treatments indicates a growing consensus among credible scientists about the potential for monoclonal antibodies to be a powerful weapon against Covid-19. They hold the distinct possibility of both preventing and treating the disease; ongoing clinical trials could show evidence of efficacy over the next several weeks, potentially before vaccine trials. Even if a vaccine is successful, such treatments will still be of enormous value. There is an ongoing debate about how to prioritise recipients of any successful vaccine, with some arguing for placing health-care workers at the head of the line. Antibodies could be part of the equation and given to frontline health-care workers to protect them from becoming infected. The challenge, however, is that bioreactors must be used to grow lines of antibody-making B cells; this could be expensive and scarce. [2] The table below show the drugs that have received Emergency Use Authorisation for use in various countries.

Table 1 – Covid-19 Emergency Use Authorisations in different countries [3]

Drug	Sponsor/ Funder	Type	Countries
Remdesivir	Gilead, NIH, USAMRIID, CDC	Anti-viral (replication)	United States, Australia, Belgium, Canada, France, Germany, Israel, Italy, the Netherlands, Romania, Spain, Switzerland and the UK under an expanded access program
Nitric oxide	Bellerophon Therapeutics,	Vasodilation/ bp	US

	Inc., Vero Biotech		
Lopinavir +ritonavir (Kaletra)	(AbbVie)	Antiretroviral (cell entry)	Israel
Itolizumab (Alzumab)	Biocon, Equillum	Anti-inflammatory	India (National Task Force on Covid-19 decided against including Itolizumab drug in clinical management protocols for treating the disease, but the DCGI approved its "restricted emergency use" in infected patients
Favipiravir	Multiple (.decimal, Zhejiang Hisun Pharma, Glenmark)	Anti-viral (replication)	India
Atlizumab (Actemra)	Roche, Chugai, Cipla (BARDA)	Anti-inflammatory	China
Angiotensin II (Giapreza)	La Julla Pharmaceutical Company	Vasodilation/ bp	UK (Specials procedure), Belgium, Italy, Germany

Better coordination, however, is still necessary to ensure that clinical trials are large and robust enough to produce decisive results. The UK benefits from a centralised health service that facilitates coordination for the large N Recovery trial, which has 12,000 patients and hundreds of participating

hospitals. [4] Meanwhile, the fragmented US health system has completed just one large trial (on remdesivir) under the auspices of the National Institutes of Health. The lack of a nationwide strategy to deal with the pandemic has affected not just testing and distribution of PPE and ventilators, but also how clinical trials are managed.

Ensuring Equitable Access to Treatment

Coordination also remains critical for global access and equity. Rich countries have purchased hundreds of millions of vaccine doses, even before they have proved successful. This situation is likely to keep happening, as evidenced by President Trump's purchase of the world's supply of remdesivir (which is made by Gilead, an American company). Defenders of Trump's move argue that this was a simple case of free market dynamics at play. [5] But such actions could give rise to governments invoking compulsory licensing, which could be legally justified because of the global pandemic. If drug manufacturers could access remdesivir's raw ingredients, then they could produce and license a generic version at a lower price point. This has not yet occurred and because pharmaceutical companies do not, in reality, want to contend with compulsory licensing, this should theoretically incentivise deals to ensure access.

Governments are taking other steps to ensure domestic supply. The UK, for example, has placed a ban on the export of dexamethasone; any wholesaler that attempts to export it to another country could lose its licence. [6] Pakistan's Punjab government is now watching the sale and distribution of dexamethasone (both oral and injectable) very closely to prevent profiteering and hoarding. No doubt the same phenomenon will occur in other countries. What mitigates the potential of total disruption in availability is the fact that the drug has been on the market for almost 60 years and is generic. Merck, its maker, no longer has exclusive rights to market it and it is produced in factories around the world.

The key point is that in the absence of global coordination, poorer countries are likely to lack access to life-saving treatments. Without rich governments taking the lead to ensure equity, other initiatives have arisen, but they lack funding and the political heft. The WHO's Covid-19 IP Pool is designed to provide equitable distribution of supplies in a way that ensures that poor countries are included. While it has the support of India, the Netherlands, Portugal, South Africa, Norway and Luxembourg, the US and major pharmaceutical companies are not participating, which limits its effectiveness. The

pharmaceutical companies argue that removing IP rights disincentivises innovation and takes away rewards for assuming risk in developing drugs and vaccines. The US government echoed those concerns. The philanthropy-backed Covid-19 Therapeutics Accelerator seeks to fill the gap in coordination efforts focused on drugs, seeking to "coordinate resources and efforts to build a drug pipeline and to remove key bottlenecks for academics, pharmaceutical companies and biotechs who have the expertise that will be needed to advance promising candidates through to commercialization." [7] To date, the Accelerator has awarded just $69.4 million to support nine clinical trials, with several focused on health workers. [8] While commendable, the scale is simply too small for what poor countries need.

While the therapeutics landscape has evolved and generated approved drugs, several drugs that are suitable for emergency use and a number of promising ones in clinical development, the politics of Covid-19 treatments remain largely unchanged. Rich governments have largely opted out of global coordinating bodies and maintain a go-it-alone stance in the face of the pandemic. What is hopeful is that repurposed drugs that are no longer under expensive patents can be purchased at more affordable

price points for poor countries. The challenge for those governments will be in finding the resources to make them available to their populations.

Annex

Table 2 – The most advanced Covid-19 therapeutics candidates [9]

Drug [10]	**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

Ultomiris (ravulizumab)	Alexion	Alexion	Phase III	Monoclonal antibody
Losmapimod	Fulcrum Therapeutics	Fulcrum Therapeutics	Phase III	Mitogen-activated protein kinase (MAPK) inhibitor
Kaletra (lopinavir/ ritonavir)	AbbVie		Phase II/IV	HIV protease inhibitor
Kevzara (sarilumab)	Sanofi; Regeneron		Phase II/III	IL-6 receptor agonist
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
RLF-100 (aviptadil)	NeuroRx; Relief Therapeutics	NeuroRx	Phase II/III	Synthetic human vasoactive intestinal peptide (VIP)
Actemra (tocilizumab)	Roche		Phase II/III	IL-6 receptor agonist
ABX464	Abivax		Phase IIb/III	HIV-1 Rev protein inhibitor
Rhu-pGSN (gelsolin)	BioAegis Therapeutics		Phase II	Recombinant human plasma
MK-4482	DRIVE; Ridgeback Biotherapeutics; Merck		Phase II	Antiviral
TXA-127	Constant Therapeutics	Columbia University Irving Medical Center	Phase II	Angiotensin-(1-7) peptide

LAM-002A (apilimod dimesylate)	AI Therapeutics, Inc;	AI Therapuetics, Inc.; Yale University	Phase II	PIKfyve Inhibitor
PRO-140 (leronlimab)	CytoDyn		Phase II	Monoclonal antibody
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
Calquence (acalabrutinib)	AstraZeneca	AstraZeneca	Phase II	Kinase inhibitor
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
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

Footnotes

1. ^ https://www.who.int/initiatives/act-accelerator/covax
2. ^ https://www.sciencemag.org/news/2020/08/designer-antibodies-could-battle-covid-19-vaccines-arrive
3. ^ https://www.bio.org/policy/human-health/vaccines-biodefense/coronavirus/pipeline-tracker
4. ^ https://www.sciencemag.org/news/2020/07/one-uk-trial-transforming-covid-19-treatment-why-haven-t-others-delivered-more-results
5. ^ https://theconversation.com/how-countries-get-away-with-hoarding-drugs-in-a-pandemic-141854
6. ^ https://theconversation.com/how-countries-get-away-with-hoarding-drugs-in-a-pandemic-141854
7. ^ https://www.therapeuticsaccelerator.org/frequently-asked-questions/
8. ^ https://www.therapeuticsaccelerator.org/investments-made/
9. ^ https://www.bio.org/policy/human-health/vaccines-biodefense/coronavirus/pipeline-tracker
10. ^ 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"

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

GENERAL ENQUIRIES
info@institute.global

FIND OUT MORE
INSTITUTE.GLOBAL