



Access to Vaccines, Therapeutics, and Diagnostics

Background paper 5
The Independent Panel for Pandemic Preparedness and Response
May 2021

The
Independent
Panel
FOR PANDEMIC
PREPAREDNESS
& RESPONSE



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This paper has been prepared by the Secretariat for the Independent Panel for Pandemic Preparedness and Response as background for the Panel. The views expressed herein do not necessarily represent the views of the Panel.

CHAPTER 1 – SYNTHESIS REPORT

Introduction

We are in the midst of a new phase of the COVID-19 pandemic, with many uncertainties remaining for the coming months.

After more than a year and a half of enduring COVID-19, despite the efforts and progress made in countering the spread, the world stands poised to move into potentially more challenging stages of the pandemic. If not confronted effectively, the results will be even more devastating.

SARS-CoV-2 is generating new variants first observed in the UK, South Africa, Brazil and elsewhere across the world: more infectious, some of them are better able to evade vaccine-induced immune response and perhaps more lethal. Infection numbers have been climbing since February 2021 and coming in waves; by April 2021 case trajectories were growing exponentially in some places. Lockdowns and curfews extend on, sapping energy and will. **COVID-19 is on its way to becoming endemic.**

It is utterly possible due to variants and waning immunity that vaccine boosters will be needed annually or every six months. This would be on the order of 5 or 10 billion vaccinations a year, or over 10 or 20 billion doses for two-dose vaccines, to be equitably and effectively distributed all over the world.

Highly efficacious vaccines are in production, in record time, and ramping up. But **they are not being distributed fairly nor in the most effective way to protect the most at-risk people across the world and suppress viral transmission.** High income countries secured more than 200% population coverage in vaccine doses. At the same time many low-income countries struggle without. These countries face unfair and exploitative arrangements on indemnity and use of sovereign assets as collateral at the request of some vaccine manufacturers. COVAX, the global mechanism established to equitably deliver vaccines, has been making good progress—even so, it is uncertain whether it will reach its target to cover 27 % of the population in LMICs in 2021, and yet the 27% target for LMICs in 2021 is well short of the coverage required for sufficient protection against variants and to control the pandemic.

Current manufacturing capacity is insufficient to produce and distribute doses across the world. It is currently concentrated in only a few regions: Europe, the US, China, Russia, and India. There is very limited capacity in Africa and Latin America. This makes it difficult for these regions to access new vaccines. This is even more of an issue in the case of producing mRNA vaccines, the platform critical for adapting to and controlling variants. In the absence of a fully-functioning, organized system for access, including adequate cold chain requirements, countries and regions are forced to fend for themselves and must continue to do so, even in the face of hoarding.

Alongside these issues, the **tests and therapies essential to controlling the pandemic remain seriously constrained, especially in low- and middle-income countries.** Oxygen supply—the low-cost and most essential treatment for severe cases thus far, together with dexamethasone—is experiencing acute shortage. Low- and middle-income countries require but are not able to provide an estimated 2.5 million cylinders per day¹, and the need is increasing daily. Despite its importance, there has not been much

¹ As of April 12, 2021 (<https://www.path.org/programs/market-dynamics/covid-19-oxygen-needs-tracker/>)

breakthrough in therapeutics. A focused, collaborative and well funded R&D for a cure against COVID is urgently needed.

While high-income countries were able to conduct an average of 533 tests per 100,000 people each day in mid-March (2021), the rate was nearly 15 times lower in lower-middle-income countries, at just 36 tests per 100,000 people. It was lower still for low-income countries at 5.5 tests per 100,000. Only 26 out of hundreds of commercialized tests and diagnostic kits have gained the WHO emergency use listing required for global distribution through the Access to COVID-19 Tools Accelerator (ACT-A). Of the 26 approved, only two of them are the antigen-detecting rapid diagnostic tests (Ag-RDTs) that are more easily scalable in low- and middle-income countries. Without test diagnostics, the efforts are flying blind: lack of testing means lack of data and insight into how the pandemic is progressing.

A. Call for urgent actions: We must act now to address serious inequity in access to the tools and build longer-term solutions to control the pandemic.

To prepare ourselves for the new phase of the COVID-19 pandemic and respond effectively, we need a strategy with clear goals, milestones, and priority actions. Also, **significant inequity in vaccine access must be addressed immediately**. It is not only unjust but threatens the effectiveness of global efforts to control the pandemic. Variants may still emerge that our vaccines cannot manage. The more quickly we vaccinate, the less likelihood of additional variants emerging. One action we should take now is the **reallocation of available vaccine doses, thereby bringing order to the current vaccine market**. **Scaling up supplies for therapeutics and diagnostic tests** is also very urgent to save lives.

Moreover, to prepare for the endemicity of COVID-19 and address inequity in vaccine access in a more sustained way, **we need to urgently build manufacturing capacity of mRNA and other vaccines in Africa, Latin America, and in other low- and middle-income areas**. Vaccine manufacturing is highly specialized and difficult. Boosting production is time-consuming. **It requires agreements on voluntary licensing and technology transfer**.

B. Call for a reset for the future: For future pandemics, we need to re-shape what exists and establish a new pre-negotiated system to accelerate R&D and achieve equitable access for the “Global Health Commons”.

ACT-A was launched on 4 May 2020 and evolved organically, creating vaccines, diagnostics, therapeutics and health systems pillars intended to be agile collaborative partnerships rather than hierarchical structures. While ACT-A was able to establish a successful platform in many respects, the fact it did not pre-exist the COVID-19 pandemic and had to be purpose-created has shown in its shortcomings. Not all its pillars have been equally successful, and a coherent, strategic, inclusive and fully funded framework has not been achieved, even to this day.

Also, ACT-A is seen by countries and civil society as **supply-driven and not inclusive enough, with large donor countries and institutions having an asymmetric influence on decision-making**. There is a **lack of shared vision among all stakeholders, including both countries and manufacturers that the therapeutics, vaccines and diagnostics needed to counter pandemics are a “Global Health Commons”**

– without this shared vision the “business-as-usual” approach² prevails. **Concentration of manufacturing capacity, and of trials and knowledge generation**, for vaccines, therapeutics, diagnostics and other essential supplies in a small number of countries has been a major contributor to inequity. Vaccine product development was most successful, though even here there was a **lack of end-to-end planning with R&D, clinical trials, and manufacturing processes guided by a goal and strategy for equitable and effective access**.

A pre-negotiated system to accelerate R&D and achieve equitable access is vital to pandemic response and the development and delivery of vaccines, therapeutics, diagnostics and essential supplies. ACT-A provides a valuable model and lessons from both its strengths and weaknesses should guide the establishment of a permanent platform which stands in readiness for any future pandemic. **The Panel recommends that a comprehensive review of the achievements, financing and governance of ACT-A is conducted. The current model of high-income-country dominated systems must be transformed to a global, inclusive approach** because it is the right thing to do and because it is the only way to manage a global pandemic.

Critically such a system needs to be able coordinate decision-making globally, maintain effective relationships with vaccine and other product manufacturers from both public and private sectors and from all regions; strengthen global and local manufacturing capacity including long-term and sustained investment in technology transfer; and incorporate a financing mechanism that invests early in the development cycle in order to support rapid, equitable access.

Leaving out any one of these elements risks undermining an effective solution. Implementing these reforms requires highest-level commitments from governments, industry and multilateral institutions. One of the key ones is a **country obligation that limits the extent to which bilateral R&D and procurement deals between countries and manufacturers undermine global solutions** and increases the use of the new global platform. These commitments could be formulated as part of a **legally-binding pandemic framework convention**, which sets out general obligations to R&D and global equitable distribution of pandemic tools, while more specific obligations, including any mechanism, financing, and governance could be set out in a protocol.

The world is still struggling with a deadly pandemic. As disorienting and terrible as the last year has been, learning to live with COVID-19 for the long haul will demand more, and understanding the current situation shows we are not prepared. We must take urgent steps to get there: action now is action taken for the future.

² This means global corporations develop and sell proprietary products designed for wealthy countries, leaving the rest of the world reliant on the goodwill of donors, on development assistance and charity to gain access — eventually—to these life-saving health technologies ([Torreale et al, 2021](#))

1. Summary of the Current State – key issues and lessons

(1) Overview of the current situation

Exceptional progress has been made in vaccine R&D: more than 80 vaccine candidates are in clinical development. Twenty-six are in Phase III or IV clinical trials. The 13 vaccines now in use have been made available within approximately 12 months, compared to conventional vaccine development which takes on average 8-10 years between drug discovery and licensure ([LSHTM, 2021](#)).

Serious inequity has emerged in vaccine procurement and actual vaccination rates: high-income countries – Canada, UK, Australia, New Zealand, EU, and US – all secured over 200% population coverage worth of vaccine doses ([Duke, 2021](#)), while many low-income countries struggle without. At the time of writing, Israel has administered 118.9 doses of vaccination per 100 population, the UAE 92.58 doses, Chile 64.13, the UK 59.08 doses, Bahrain 58.14, doses, the US 57.49 doses, etc., while vaccinations are just beginning, or yet to begin, in many low-income countries ([Our World in Data, 2021](#)).

Despite good progress through COVAX, coverage for low- and middle-income countries is lacking: COVAX expects approximately 1.8 billion doses to be available to 92 low- and middle-income countries before the end of 2021, which covers 27% of the population of low- and middle-income countries ([COVAX, 2021](#)). This will allow for coverage of healthcare workers and a number of people most at-risk. Clearly, this 27% is well short of the coverage required for sufficient protection against variants and to control the pandemic. Many people may have to wait until 2023/2024 for vaccination ([Duke, 2021](#)). Moreover there are many uncertainties affecting 2021 supply, including the quantity needed, in particular if boosters are required at least annually, manufacturing capacity, regulation, funding availability, final contract terms and, in some cases, the readiness of countries to begin their national COVID-19 vaccination programmes. COVAX had been expecting to distribute almost 100 million doses by the end of March 2021. Due to a marked reduction in supply it has only been able to distribute 38 million doses ([WHO, 2021](#)).

Serious shortages and geographic concentration of manufacturing capacity is contributing to inequity and threatens the effectiveness of vaccination efforts. Upper bounds for vaccine production capacity in 2021, across all vaccine technology platforms, is estimated at 14 billion doses ([UNICEF, 2021](#)). This is a highly optimistic view: it assumes all vaccine candidates will be successful and produced as planned, which is unlikely given recent challenges faced by a few major vaccines such as capacity and supply chain constraints, lack of raw materials, and uncertainties around thrombosis related issues. Current manufacturing capacity, based on publicly available data ([Knowledge Ecology International, 2021](#); [Third World Network, 2021](#)), is focused in a few regions (Europe, US, China, Russia, India, etc.). There is very limited capacity in Africa and Latin America. This makes it difficult for these regions to access new vaccines. As COVID-19 trends towards endemicity, and an increasing number of variants enter the scene, the world's population will likely need multiple vaccinations on an ongoing basis. It is estimated that ~5.3 billion vaccine doses are required for a single-dose vaccine, or possibly 12–16 billion in case of a multi-dose vaccine (Frederiksen et. al., 2020), and this will likely be required annually or every six-months as boosters, depending on the duration of the protection they provide and the emergence of variants.

The already-concerning progression of viral mutations may be accelerated by insufficient doses and untimely administration of vaccines. Some mutations can significantly compromise the effectiveness of the vaccines and accelerate the spread of the disease. There are three major variants currently circulating. While B.1.1.7, first seen in the UK, has emerged as a more transmissible and quickly spreading variant (now identified in 82 countries), it is not notably resistant to vaccine-induced neutralizing antibodies, and researchers have substantial confidence that these variants will not affect the efficacy of the present generation of vaccines ([Garcia-Beltran et. al., 2021](#)). That said, there is a realistic possibility that infection with the B.1.1.7 variant is associated with an increased risk of death compared to infection with non-VOC viruses ([Horby et. al., 2021](#); [Challen et. al., 2021](#)). The other two – B.1.351 and P.1, first identified in South Africa and Brazil, respectively – are raising vaccine efficacy concerns ([Moore, 2021](#)) (See Table 1 of Chapter 2 for efficacy profile of main vaccines against variants).

Also despite 600 potential therapies in various stages of development ([BioWorld, 2021](#)), **R&D for therapeutics has not yet resulted in any outstanding efficacious treatments.** Thus far dexamethasone and oxygen therapy are the best we have for the treatment of severe cases. **Oxygen therapy is suffering from a lack of strategic prioritization, despite its critical importance.** As of April 11, 2021 the need for oxygen amongst all low- and middle-income countries amounts to 2.5 million cylinders per day at an estimated annual cost of USD \$3.68 billion. Even so a number of other therapies show recent promise—including early treatment with monoclonal antibodies³—as outlined in the detailed report for therapeutics and diagnostics below. The United States is now calling for priority advancement of candidates that show potential for being broadly neutralizing (i.e., likely to be effective against new variants), easily administrable and have reached phase two clinical trials, with proven safety profiles.

Insufficient availability and access to diagnostic tests and their quality are major limitations to current efforts against the pandemic. Although over 1000 tests and 177 antigen rapid diagnostic tests (Ag-RDTs) have been commercialized ([FIND, 2021](#)), only 26 tests, including 2 Ag-RDTs, 23 molecular tests, and 1 antibody test have been granted WHO emergency use listing. This is a pre-requisite for provision through ACT-A ([WHO, 2021](#)). Regulatory capacity needs to be strengthened to improve assessment of novel diagnostics. In addition to highly variable quality of tests, there are serious shortages and inequities in access to them. Of the 900 million tests required for 2021, 120 million tests have been reserved for LMIC purchase through volume guarantees. While high-income countries were conducting an average of 533 tests per 100,000 people each day in mid-March (2021), in lower-middle-income countries the rate was almost 15 times lower, at just 36 tests per 100,000 people, and lower still for low-income countries at 5.5 tests per 100,000 ([FIND, 2021](#)).

(2) Key lessons learned across the value-chains for vaccines, therapeutics, and diagnostics

a. Governance and coordination

ACT-A is the only multilateral initiative to accelerate development, production, and equitable access to COVID-19 tests, treatments, and vaccines. The concept brings together governments, scientists, businesses, civil society (CSO group, [2020](#)), philanthropists and global health organizations. It includes the Bill & Melinda Gates Foundation, CEPI, FIND, Gavi, The Global Fund, Unitaid, Wellcome Trust, the WHO, and the World Bank.

³ Though some preliminary studies show reduced efficacy against variants, and there will be cost and logistics constraints especially in resource constrained settings.

Overall governance

While ACT-A demonstrates an unprecedented level of collaboration among key institutions, it is seen by countries and CSOs as **supply-driven and not inclusive and transparent enough**. Not strong enough involvement of China, Russia, and India, and many other low- and middle-income countries and delayed participation of the US government, have significantly limited the scope and acceptance of ACT-A as a “global mechanism”. As the mechanism established itself during the emergency, it deliberately relied on the decision-making mechanisms of existing organizations. Many of these are built on what is seen by some as a **donor support and driven model**: this means large donor countries and institutions have asymmetric influence on decision-making. **This must be transformed to a global, inclusive approach** because it is the right thing to do and because it is the only way to manage a global pandemic.

Shared vision and industry policy

There is a lack of shared vision among countries, manufacturers and related organizations that the therapeutics, vaccines and diagnostics needed to counter pandemics are a “Global Health **Commons**” that must be available for all countries to ensure collective protection and eventually protect each country’s own citizens. In the absence of such a shared vision and in the urgency in which decisions had to be made, a “business-as-usual” market-based approach was taken. This means global corporations develop and sell proprietary products designed for wealthy countries, leaving the rest of the world reliant on the goodwill of donors, on development assistance and charity to gain access — eventually—to these life-saving health technologies ([Torreele et al, 2021](#)). However, the use of public funds must be for the largest public return on investment. Industrial policy must be re- designed and pre-negotiated to secure equitable access to these new tools in the face of a pandemic.

Financing

Insufficient and delayed financing is one element at the core of the failure to secure global access to life-saving health technologies. It affects all parts of the value-chain for each product/countermeasure. With limited and delayed funding, COVAX was not able compete with high income nations either hosting big manufacturers or with greater purchasing power ([Nature, 2021](#)). Israel’s willingness to pay a higher price, reportedly \$30 per dose for the Pfizer/BioNTech vaccine, has been cited as one reason for the rapid scale-up of its vaccination program ([Regev, 2021](#))⁴. Specifics of purchase agreement details are secret, but the limited information available points to variation in prices and high price signals ([Loftus, 2020](#)).

The funding shortage has been even more serious for therapeutics and diagnostics. Due to the shortage of funds, the ACT-A diagnostic pillar was unable to use a volume guarantee secured for quality Ag-RDTs. How decisions are made to allocate funds is not always clear. Overall, \$27.2 billion is said to still be needed for ACT-A Strategic Priorities in 2021. An estimated additional \$30 billion is required if considered in total: meeting needs for addressing variants, increasing vaccine coverage from 20% to 80% in advance market commitment-covered countries, expanding testing in low- and middle-income countries to 90% of HIC rates and treatment coverage proportionally to testing ([WHO, 2021](#)).

End-to-end strategy

Although the R&D success for vaccines was extraordinary, the global effort by ACT-A/COVAX to make vaccines available to people has been driven **without a clear global vaccination strategy** for all countries and citizens and agreed by all actors. For example:

⁴ Other factors include its small population and a commitment to access to data from its vaccination rollout.

- R&D is focused on making vaccines available as fast as possible rather than on adherence to target product profiles that consider use in low- and middle-income country context (e.g. requiring ultra-cold chain);
- Vaccination plans are constrained by a lack of transparency around pricing, supply availability and delivery timing, and non-disclosure agreements with unreasonable terms, which in turn limit the ability of countries to plan ahead.

The lack of a clear strategy to navigate R&D and manufacturing also applies to diagnostic tests. The development and application of technical product profiles (TPPs) based on the kind of tests wanted, including specifications for sensitivity and specificity, should have been established early on and were not (see R&D Lessons Learned within In-Depth Therapeutics and Diagnostics paper for more on TPPs). This was compounded due to WHO's technical leadership being weaker in the area of diagnostics and therapeutics, without clear leading organizational units.

Health Systems Connector (HSC)

The HSC suffered significantly from lack of clarity and agreement on objectives and strategic leadership. HSC is meant to cut across the work of all ACT-A pillars with a strong focus on country level roll-out of new vaccines, therapeutics, and diagnostics. Interviewees consulted in the course of the Panel's work consistently saw the HSC as "most dysfunctional" among the four pillars. It experienced tensions and confusions in objectives inside the HSC, with WHO focusing on longer-term system issues and other participants aiming to solve the immediate crisis. Important lessons include upfront agreement on very clear objectives, deployment of the teams aligned with the objectives, and WHO's focused role in normative technical guidance rather than operational responsibilities.

b. R&D

Excessive focus on speed over global public health values

As a result of an almost-exclusive focus on speed, major vaccines produced are not necessarily fit for global access and have not fully followed Target Product Profiles (TPPs) established under the WHO R&D Blueprint for Covid vaccines (e.g., requiring ultra-cold-chain, lack of technical know-how for various platform technologies, etc.).

Weak clinical trial coordination and capacity—including a lack of well-distributed regional trial sites (including in low- and middle-income countries), the absence of vaccine trials comparing effectiveness of currently available vaccines head-to-head ([Cohen, 2020](#)), and poor therapeutic pipelines and integration with trials—results in poor quality trials with limited actionable findings.

Vaccine developers designed the endpoints for trials in order to gain faster registration. None of the trials (as of Oct 2020) were designed to detect a reduction in clinically and public health-salient outcomes such as viral transmission, hospital admissions, use of intensive care, or deaths. Nor were the vaccines being studied to determine whether they could interrupt transmission of the virus. ([Doshi, 2020](#)). While regulators around the world changed processes to speed R&D and regulatory pathways, there are many more opportunities for greater efficiencies, better use of tools, improved data-sharing and more coordinated approaches.

Slow approvals

There remains a **need for more Ag-RDTs** that meet technical specifications and can be manufactured at scale to achieve WHO EUL. This is necessary for ACT-A to deploy Ag-RDTs based on other well-established regulatory authority approvals. Developers of the two approved Ag-RDTs reported that demand from HICs could have absorbed supply “several times over” leaving limited volumes for low- and middle-income countries without volume guarantees from ACT-A.

Financing and institutional leadership

Financing and support by US BARDA and CEPI, as well as past scientific investments (e.g., in mRNA technology) played a significant role in the success of vaccine R&D for multinational pharma companies. However, HICs directly funded vaccine R&D to help secure supply for themselves ([So & Woo, 2020](#)), which further weakened CEPI’s and COVAX’s ability to negotiate with manufacturers. In contrast, **therapeutics have suffered from lack of CEPI-like leading institutions** as well as structural underinvestment and undervaluing. The diagnostics pillar within ACT-A relies on the Foundation for Innovative New Diagnostics (FIND), which plays a similar role to CEPI. But FIND is significantly underfunded.

WHO’s role

The WHO’s R&D blueprint served to establish a common R&D agenda quickly. It was most effective in support for vaccine product development and to a lesser extent in diagnostics, while therapeutics trialing, development of a systematic evidence base for public health interventions, and measures to ensure equitable allocation were less successful. Despite the successful achievement of the Solidarity trial, interviewees described the management of clinical research programs by WHO as being partly out of their purview, area of expertise and core functions. It also creates conflict of interest. It was suggested that the focus of WHO should remain on developing guidelines, setting standards (e.g., trial design), pre-qualification (PQ), allocation frameworks, and providing leadership, being the convener and coordinator.

c. Manufacturing

Limited sharing/transfer of technology and patent licensing by vaccine producers

This is a significant issue which must be addressed in the current pandemic and avoided in future pandemics. The world will require large numbers of vaccines in the years to come. Platforms and tools to enable technology transfer, such as the COVID-19 technology access pool (C-TAP), the Medicines Patent Pool (MPP), and the WHO vaccine technology transfer hub have not been effectively utilized so far. The IPR/TRIPS waiver proposed by South Africa and India is supported by two-thirds of WTO member countries, but as at March 2021 it had not been supported by a number of HICs such as the US, UK, in the EU, Canada, and others. Proponents suggest that it will expand production of COVID-19 health products including vaccines, secure lower prices, and speed their equitable distribution. Opponents argue that actual limitations are related to technical capacity and not IP, and that IP waivers would stifle innovation. These issues have not yet surfaced for therapeutics due to lack of effective products. This could, however, become a critical issue in the near future in the case of monoclonal antibodies and for future pandemics. **There need to be incentives for manufactures to engage in voluntary IP licensing and technology transfer, through industry policies, negotiated deals, and country agreements/obligations.** Agreement among countries on effective approaches is urgent and critical for boosting and maintaining manufacturing capacity.

Lack of machinery

There is no agency mandated to finance and strengthen manufacturing capacity for vaccines, therapeutics, and diagnostics. **Expanding regional capacity for key platform technologies (e.g. mAbs, mRNA, etc.) to avoid reliance on few manufacturers and fortify supply systems** will be a priority moving forward. This will be difficult and time-consuming to do well, but it is necessary, and requires more than transferring intellectual property for vaccine formulas or voluntary licensing. It requires transfer of highly specific and specialized technology and know-how, in coordination with regulatory oversight, robust participation of vaccine developers and application of good consistent lab-level biological manufacturing practices. Given the significant challenges, a strong system is required to accelerate the progress, which is currently missing.

d. Procurement

Clear playbooks with complementary roles among key institutions

Regional institutions have emerged as important units for pooled procurement and negotiation, information sharing, technical assistance, and rapid response to country needs – for example, Africa CDC played an important role in these functions. There are strong country demands for such regional capacity as countries, particularly low- and middle-income countries, do not have access to technical and market expertise and reliable information as a basis on which to negotiate with manufacturers. Such regional capacity has been lacking in Asia and there is room for further strengthening for Africa and Latin America. Addressing this could alleviate some of the serious inequities in procurement and manufacturing challenges outlined previously.

Gavi is playing a specific role in COVAX for vaccine procurement. However, there are **no well-funded institutions with procurement mandates for therapeutics and diagnostics**. The Global Fund has been playing a role beyond its original mandate to fill this gap, deploying \$1 billion through its COVID-19 Response Mechanism (C19RM) in 2020. It recently secured significant new funding (\$3.7bn) to help meet procurement needs. But clarity in institutional leadership, and strengthening of expertise, is required for future pandemics.

The World Bank funded country procurement of scarce commodities with a significant funding commitment (\$6 billion for initial response, and \$12 billion (of which \$2 billion had been approved as of April 20, 2021) for vaccine response), while at the same time the ACT-A pillars tried to centralize procurement with equitable distribution. This created competition between the two, and the lack of coordination hurt response efforts. Further clarity on the roles of the Bank and other development banks including potential reforms of their funding approach are needed, which will require an objective assessment of the Bank's support to COVID-19 responses including a review of options for the Bank to finance global public goods such as vaccines, therapeutics, diagnostics, and other essential supplies.

Procurement of raw materials

Beyond the procurement challenges associated with core countermeasures, there were challenges in procuring raw materials ([Kay, 2021](#)), as well as reagents necessary to operate vaccinations and diagnostics, etc. Testing requires reliable supplies of a range of materials, including swabs, transport media, reagents, primers, assays, and PCR machines ([Rajan et. al., 2020](#)). There is a need to support secondary supply-chains for these materials.

e. Allocation and Delivery

Flexibility tailored to epidemiology

The [current allocation mechanism for COVAX](#) that follows the initial WHO recommendation establishes two key phases for recipients. Phase 1 consists of the proportional allocation of 20% of the population until all countries are covered to this level (now actually estimated at ~27%). Once this is achieved, Phase 2 will take a more epidemiological approach, consisting of weighted allocation dependent on the proportional coverage (%) requested beyond the initial 20%, and the consideration of vulnerability and COVID-19 threat ([WHO, Dec 2020](#)). There needs to be more flexibility tailored to epidemiology and strategic phases in allocation of vaccines, therapeutics, and diagnostics.

Transparency and communications to facilitate country planning

In addition to the inequities highlighted above, countries say that they are receiving **passively delivered information** on vaccine allocation without knowing when doses will arrive. This makes the planning of vaccination extremely difficult. **The lack of communication**—as well as the recognition that 20-27% coverage will not be adequate to tame the pandemic—are factors that have led to countries seeking alternative supply arrangements outside of ACT-A/COVAX.

Integrated view including non-western providers

Russia, China and India are using bilateral SARS-CoV2 vaccine donations and deals to strengthen alliances with multiple low- and middle-income countries ([Cullinan & Nakkazi, 2021](#)). China reports that it has offered vaccine assistance to 53 developing countries, and more than 10 million doses of the Chinese vaccines have been administered overseas since the end of 2020 ([China Daily, 2021](#)). It also agreed to help Egypt and Indonesia to be manufacturing hubs in the regions. Meanwhile, by 25th February, Sputnik V of Russia had been registered in 37 countries, including a number in Africa. At least 11 Latin American countries have also received Sputnik V. Russia has also licensed manufacturing companies to produce its vaccine in India, Brazil, China, South Korea, and Argentina. India has donated free vaccines to at least 13 countries and provided ~58 million doses to other countries, on a free and commercial basis ([Kapur, 2021](#)).

Although it is too early to draw lessons on delivery of vaccines, significant challenges in distribution, administration, and uptake (with vaccine hesitancy) are expected. This highlights the importance of preparedness and systems building in peace time. High-level global political dialogues on vaccine supply and deployment have been insufficient, despite its critical importance. Significant inequity and inefficiencies in global vaccination are going unaddressed.

2. Urgent needs to control the current pandemic

To prepare ourselves for the new phase of the COVID-19 pandemic and respond effectively, we need a strategy with clear goals, milestones, and priority actions. Also, significant inequity in vaccine access must be addressed immediately. It is not only unjust but threatens the effectiveness of global efforts to control the pandemic. Variants may still emerge that our vaccines cannot manage. The more quickly we vaccinate, the less likelihood of additional variants emerging. One action we should take now is the reallocation of available vaccine doses, helping to bring order to the current vaccine market. Scaling up supplies for therapeutics and diagnostic tests is also very urgent to save lives in low- and middle-income countries.

Moreover, to prepare for the endemicity of COVID-19 and address inequity in vaccine access in a more sustained way, we need to urgently build manufacturing capacity of mRNA and other vaccines in Africa, Latin America, and in other low- and middle-income areas. Vaccine manufacturing is highly specialized and difficult. Boosting production is time-consuming. It requires agreements on voluntary licensing and technology transfer. Such capacity must be built for now and the future: it must have flexibility to allow nimble shifting to mass volumes of product (vaccines, therapeutics, diagnostics, PPE, etc.) for emergencies at low changeover cost. Sites should be capable of self-sustained production in peace time for other priorities (e.g. poverty-related and neglected diseases: PRNDs) including through public-private partnerships.

3. For the future system

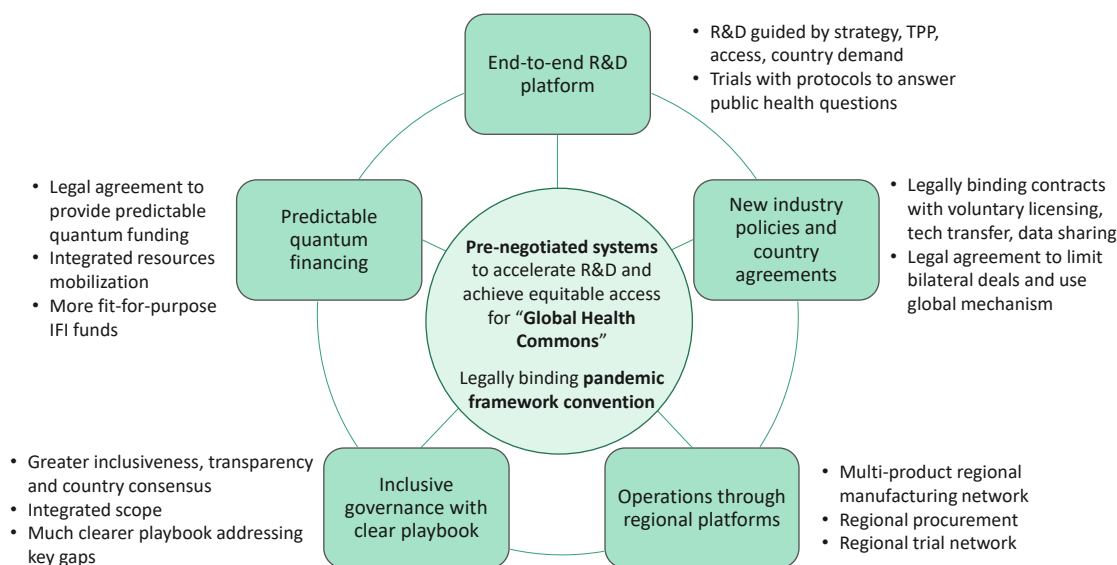
ACT-A provides a valuable model and lessons from both its strengths and weaknesses and should guide the establishment of a permanent platform which stands in readiness for any future pandemic. **For future pandemics, the current model must be transformed to a global, inclusive approach. We need to establish a new pre-negotiated system to accelerate R&D and achieve equitable access for a “Global Health Commons”.** To do so, a **thorough assessment of the ACT-A is needed, including COVAX,** building on the analyses covered in this paper.

Our analysis shows that five main shifts are needed for a potential future system, which are:

- (1) Moving away from an ‘as-we-go’ supply-driven approach to pandemic vaccines, therapies and diagnostics. End-to-end platforms should be used instead, with R&D, clinical trials, and manufacturing processes guided by a strategy for equitable and effective access from the beginning;**
- (2) shifting from “business-as-usual” health innovation designed for wealthy countries to health innovation governed by industry policies and country agreements toward equitable access;**
- (3) from operations concentrated in limited countries to operations through geographically distributed regional platforms;**
- (4) from ad-hoc coordination mechanisms with institutional gaps and tensions to pre-negotiated inclusive and transparent governance with clear playbook; and**
- (5) from fund-raising as-we-go to a predictable financing mechanism.**

These proposed shifts are tied to each other. Missing any one element risks undermining an effective solution (Figure 1). Implementing these reforms requires highest-level commitments from governments, industry and multilateral institutions. This can be formulated as part of a **legally binding pandemic framework convention.**

Figure 1: Proposed five key elements for future pre-negotiated systems for a “Global Health Commons”



The subsequent sections provide detailed considerations related to above five shifts.

(1) End-to-end R&D platform

Despite having achieved historic success in developing effective vaccines in record time and CEPI's best intentions, the R&D process was mostly supply-driven and focused on making vaccines available for a competitive commercial market, mainly in HICs. This needs to be shifted to having an **end-to-end process where R&D, clinical trials, manufacturing, and procurement are guided by a goal and strategy of equitable and effective access to a "Global Health Commons"** from the start. A few important examples are highlighted below:

- **Strategy-led portfolio approach to R&D:** The independent prioritization and simultaneous development of multiple candidates must be carried out in alignment with country demand, clear testing, treatment, vaccination strategies, and TPPs ([Bulc & Ramchandani, 2021](#)). This will minimize risks associated with product failures and facilitate a greater number of appropriate products for all settings, in particular for low- and middle-income countries (e.g., rural, off-grid, easier routes of administration - oral vs. IV, etc.). The WHO's R&D Blueprint for COVID-19 ([WHO, 2020](#)) and the coordinated global Research Roadmap ([WHO, 2020](#)) were seen as being instrumental in guiding R&D priorities and should be developed and used further. It is WHO's role to support this function.
- **Clinical trials guided by public health questions:** Clinical trials should answer the right public health questions based on high-quality, standardized protocols as opposed to those focused on obtaining regulatory approval. They should engage in head-to-head comparisons of products. This requires effective central coordination across trials; prioritizing what candidates to test; managing partnerships with regulators and manufacturers; and making data transparent through a data sharing hub.

(2) New industry policies and country agreements

At the Vaccines Roundtable conducted as part of the Panel's work program, there was consensus that the international COVID-19 response failed to direct the industry towards equitable access and effective use of vaccines in the face of vaccine nationalism and profiteering. This could also be the case for therapeutics when effective treatments are developed for COVID-19, and/or if therapeutics are the primary tool in the case of future pandemics.

In making change for the future, systems need to incorporate **rules and industrial policies to deliberately govern the collaboration between public and private sectors. This must cover incentives and financing, and clarify roles, responsibilities, and liabilities**. The following should be key elements of the industry policies and country agreements:

- **As part of the new global mechanism described below, pre-negotiate legally binding contracts for pandemic emergencies with key manufacturers, based on an agreed trigger (e.g., PHEIC). The contracts could include: (i) once-off or real-time manufacturing capacity for diagnostics, therapeutics, and/or vaccines for the global mechanism; and (ii) provision of voluntary licenses and technology transfer to generic manufacturers⁵. Such contracts should include use of the Technology Access Pool (TAP) under the global taskforce that builds on C-TAP⁶ and Medicines Patent Pool (MPP), as well as the WHO Technology Transfer Hub⁷ (See the Panel's commission background paper on scaling up vaccine production capacity for details).**
- **Be prepared for the use of compulsory measures, such as an IPR/TRIPS waiver with a requirement to share technology know-how, as required. This, if agreed by WTO member countries, can address both IP licensing and technology transfer more directly. However, attaching an IPR/TRIPS waiver to a PHEIC declaration may result in political pressure to dissuade a declaration given the anticipated impact of the waiver on manufactures, including from non-impacted States. Reforms on procedures for declaration including clearer criteria and transparency in decision-making may reduce this potential risk. The use of this approach for future pandemics, including the timing of the waiver (e.g., 3 months of no action on the voluntary approach mentioned above), should be pre-negotiated among countries and key manufacturers.**
- **Re-design COVAX as a truly global approach to influence industry with country agreements: The more the funding COVAX has with participation from HICs prior to and at the beginning of pandemics, the more vaccine doses and better terms for the world (e.g., volume guarantees, manufacturing capacity, favourable pricing, etc.) COVAX can secure. Agreements under the pre-negotiated system would need to include countries' commitments/obligations to obtain**

⁵ This will be subject to predefined terms including adequate remuneration, paid by HIC governments or HIC manufacturers for HIC manufacturer licensees or, for LMIC manufacturers, by LMIC governments or from internationally sourced funding.

⁶ C-TAP was established on May 29, 2020 by WHO to facilitate the actual transfer of intellectual property – including know-how, data, material and technology – needed to scale up production of Covid-19 health products. Unlike bilateral agreements, the voluntary licensing to be negotiated by the C-TAP is non-exclusive and open to all who can produce vaccines.

⁷ It provides vaccine producers in developing countries with the necessary know-how and technical assistance and financing. It was established in 2008 for influenza vaccines, and has been successful in expanding production capacity of influenza vaccines in 11 countries in all WHO regions.

diagnostics, therapeutics, and vaccines from the global system and limiting bilateral deals with manufacturers through a Framework Convention for Pandemics.

(3) Operating through regional platforms

Concentration of manufacturing capacity for vaccines, therapeutics, diagnostics and other essential supplies (e.g., PPE) in a small number of countries has been a major contributor to inequitable access. There is also a need for geographically distributed adaptive clinical trial networks for high quality trials. In addition, regional institutions became an important unit for procurement of tools and essential supplies. Reflecting these needs and opportunities, the future pre-negotiated system must shift to trials, manufacturing, and procurement through decentralized regional platforms:

- **Regional manufacturing network:** High-income countries (e.g., US, Canada, Europe) and emerging economies (e.g., China, India, Brazil) are investing in vaccine manufacturing capacity in response to the COVID-19 pandemic. Several experts suggested a need for piggybacking on such investments to secure a portion of manufacturing capacity for a global mechanism and aggregating global manufacturing capacity as a network.
- In addition to piggy backing on investments in HICs, the new global mechanism must deliberately support the strengthening of the manufacturing capacity in Low- and middle-income countries. For example, African Union (AU) and Africa CDC established the Partnership for African Vaccine Manufacturing (PAVM). They call for mRNA platform for vaccines in Africa, and aims to establish at least five regional vaccine production hubs as well as fill and finish capacities (Nkengasong, 2021). Significant challenges ahead include aggregating reliable demand to meet competitive economies of scale, access to finance, regulatory strengthening and harmonization across countries, talent and know-how, and infrastructure (e.g., power and water) (AU & Africa CDC, 2021). Regional institutions, WHO, and the private sector should jointly develop plans for each region, with commitments and processes for technology transfer, supported financially by concessional lending by regional and other development banks.
- **Regional procurement:** In addition, as discussed above, regions emerged as an important unit for pooled procurement, information sharing, and rapid response to country needs. The African Union (AU) is advanced in building some of these systems and capacities, with interviewees suggesting the need for similar mechanisms and capacity in other regions (e.g., Latin America - PAHO, Asia - ASEAN Centre for public health emergencies and emerging diseases – to be established). This can be an important complementary system to the global mechanism in future pandemics. The future global mechanism must support the strengthening of market expertise, quality assurance capacity, and data sharing as part of its global procurement strategy.
- **Regional clinical trial network:** Clinical trial sites need to be well-distributed including in Low- and middle-income countries. The future global mechanism must work with regional institutions to map out, strengthen, and track the network that can be a critical research capacity for other public health purposes during the peace time.

(4) Inclusive governance with clear playbook

As discussed above, the current coordination and decision-making mechanisms for ACT-A and COVAX face strong criticisms from countries and CSOs. A **new reshaped structure is needed**, building on the lessons learned from ACT-A and COVAX. The following summarizes key issues that the future system would need to address, emerging from interviews and the Roundtables – **a thorough evaluation of the ACT-A is recommended** to facilitate the decision-making on the detailed re-design:

- **Greater inclusiveness, transparency and country consensus:** The current system is seen by low- and middle-income countries, major vaccine producing countries, and CSO groups as not inclusive and transparent. This need to be re-examined and re-designed. A future potential mechanism/platform would need to include representation from Low- and middle-income countries, CSOs, countries with key manufacturers (e.g., China, Russia, India), high-income countries, and private manufacturers. It also requires effective ways of communication with stakeholders to make their voice heard. Whether it needs to be a legal structure as well as what decision the mechanism/platform should make must be examined through the evaluation of the ACT-A and COVAX.
- **Integrated scope:** As with ACT-A, the concept of having an end-to-end coordination mechanism, better balanced across vaccines, therapeutics, and diagnostics continues to receive consistent support. Some also suggest having PPE, oxygen and other essential supplies as additional pillars, given their importance. The coordination of clinical trials could be considered as part of this overarching mechanism.
- **Much clearer playbook:** The above analysis and following chapters highlight critical gaps across the end-to-end value chain – e.g., R&D for therapeutics, at risk manufacturing across all products, procurement for therapeutics and diagnostics (Global Fund is covering them without a clear mandate), oxygen, PPE – as well as need for better integration of the World Bank and regional institutions, and more focused roles for WHO. The new mechanism/platform must establish a much clearer playbook with deliberate strengthening of key institutions.

(5) Predictable Financing

Equipping a new global mechanism with significant upfront funds to counter nationalism for rapid response, as well as strengthening global manufacturing capacity and meeting other financing needs for pandemic preparedness, would require an increased scale of funding.

To meet this significant financing need, as part of broader financing needs for pandemic preparedness and rapid surge response, the Panel has recommended creating a new International Financing Facility for Pandemic Preparedness and Response (IFFPPR). The facility should be built on the following principles:

- **Capacity to mobilize long term (10-15 year) contributions of approximately \$5-10B p.a. to finance ongoing preparedness functions and with the ability to disburse up to \$50-100B at short-notice by front loading future commitments in the event of a pandemic declaration. The resources should fill gaps in funding for global public goods (including vaccines, therapeutics, diagnostics, and**

essential supplies) at national, regional and global level in order to ensure comprehensive pandemic preparedness and response.

- Agreed upon contributions based on ability to pay where larger and wealthier economies will pay the most, preferably from non-ODA budget lines and additional to established ODA budget levels.
- The Global Health Threats Council (See the main Panel report for details) to have the task of allocating and monitoring funding from this instrument to existing institutions in service of the goal of pandemic preparedness and response. Funding flows could be pre-allocated according to function and institution.
- Surge financing in the event of a new pandemic declaration should be guided by prearranged response plans for the most likely scenarios, though flexibility would be retained to adapt based on the threat.
- Secretariat for the facility to be a very lean structure, with a focus on delivering additional resources to existing organizations.

Making significant existing funds from International Financing Institutions (IFIs) more fit-for-purpose during pandemics would also be critical. For example, the World Bank committed \$12 billion and approved \$2 billion (As of April 20, 2021) for vaccine procurement and delivery. However, how this commitment can be used effectively under the current constraints of IDA and IBRD funding is still unclear, and there have been tensions between its country financing and global pooled funding through Act-A. **The Bank should assess its financing approach to COVID-19 including essential supplies and tools, and reconfigure it to make the most out of such large funding.** The result can inform the efforts of other development banks.

(6) Framework Convention for Pandemics with a Protocol for pandemic tools

Making aforementioned areas of possible reform happen would require significant political commitment by countries. As discussed above, establishing a potentially new/revised global mechanism needs to be considered. Establishing a multilateral mechanism also provides an opportunity to commit countries to new norms to enable global equitable distribution and remove barriers to multilateral efforts, such as bilateral agreements or the use of export controls.

One option raised by experts is the adoption of a **legally binding Framework Convention for Pandemics**, solidifying the commitment of countries. This could contain broad obligations, including committing to global equitable access of pandemic tools and financing mechanisms through a parallel Protocol. This new international instrument/s could include:

- **Governance:** Establishing a permanent coordination structure, such as a Secretariat, Conference of Parties, and other high-level bodies as appropriate;
- **Data sharing:** Legally binding obligations and standards around data sharing for R&D;
- **Specific country obligations to achieve equitable access:**
 - Participate in the mechanism for obtaining diagnostics, therapeutics, vaccines, and essential supplies;
 - Limit bilateral deals with manufacturers that undermine achieving coverage of a set percentage of the population or high-risk groups;
 - Limit the use of export controls that prevent manufacturers from supplying the mechanism;

- Include obligatory provisions for the sharing of products with the mechanism and voluntary licensing and technology transfer when investing public resources in R&D;
- Commitment to negotiate with industry for technology transfer using Technology Access Pool (TAP) within the new mechanism, WHO Technology Transfer Hub, and voluntary IP licensing.
- Financing: Regular annual funding (“cost of preparedness”) + ability to rapidly mobilise funds in emergencies; funding for the mechanism/platform purchases as required.
- Manufacturing network: Develop and sustain a strong regional manufacturing network for vaccines, therapeutics, diagnostics and PPE and address other areas across the R&D value-chain (R&D, procurement, delivery, etc.) by regularly taking on existing challenges (e.g. PRNDs) and outbreaks.

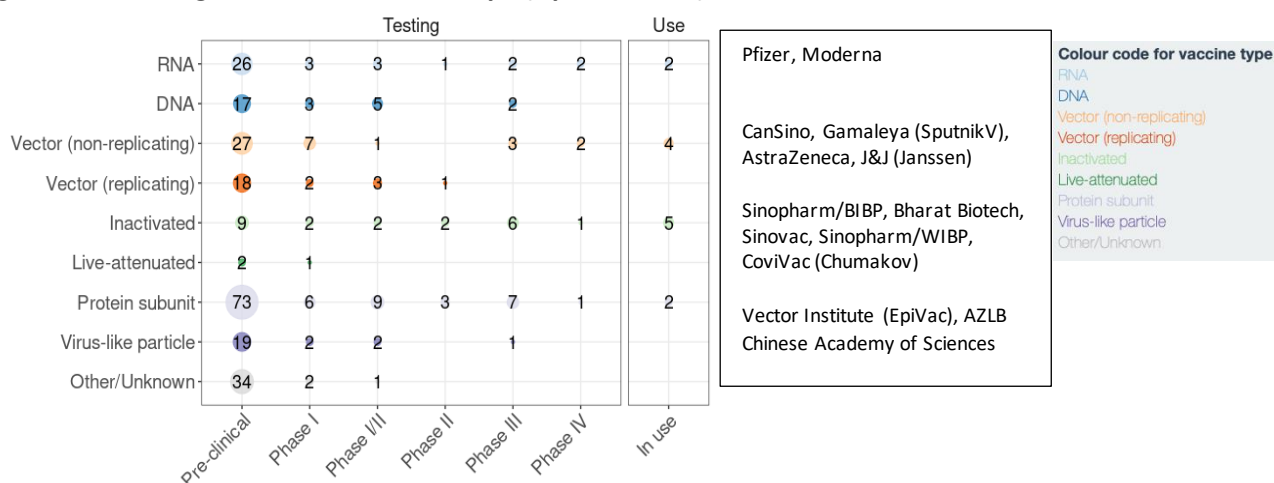
CHAPTER 2 – IN-DEPTH REPORT ON VACCINES

1. Overview of the current state

(1) R&D Landscape – Remarkable scientific achievement with concerns about new variants

The current vaccine landscape (Figure 2) consists of more than 200 candidates against COVID-19, including over 80 in clinical development with 26 of them in Phase III or IV trials (see R&D section for further details). Thirteen vaccines are already in use at the time of writing, representing a mix of vaccine platform technologies. This was achieved in just 12 months, whereas conventional vaccine development takes an average of 8-10 years between drug discovery and licensure (Røttingen, 2020). This demonstrates unprecedented scientific achievement.

Figure 2: R&D Progress – Vaccine Landscape (April 23, 2021)



Source: [LSHTM Vaccine Tracker](#)

Of the vaccines in use, the Pfizer/BioNTech vaccine is being used most widely. It has gained full or emergency use authorization (EUA) in numerous countries, mostly across North America, Europe, and the Middle East. This is the case even as its use introduces logistics challenges in many parts of the world, given the vaccine's ultra-cold storage requirements (-60°C to -80°C). Its distribution is hence concentrated in upper income countries with stronger logistics systems. It was the first vaccine to be granted EUA by the WHO on December 31, 2020, followed by two versions of the AstraZeneca/Oxford vaccine on February 15, 2021 ([WHO, 2021](#)), one produced by AstraZeneca-SKBio in South Korea and the other by the Serum Institute of India. WHO is 'expediting' other emergency approvals with anticipated decision dates over the coming weeks and months, including for several western and Chinese manufactured vaccines. Poorer countries may well then be able to expand their inoculation programs ([WHO, 2021](#); [Reuters, 2021](#)). Several poorer nations relying mostly on WHO authorizations due to limited regulatory capacity of their own, and WHO EUL is a prerequisite for COVAX Facility vaccine supply. As of March 10, 2021, COVAX had shipped over 17.8 million COVID-19 vaccines to at least 19 countries ([GAVI, 2021](#)). Ghana was the first country to receive vaccines through COVAX on February 24, 2021.

Some vaccines already in use got a head start: China and Russia authorized their own vaccines in July and August 2020 while trialling was still ongoing. These countries have administered millions of doses at home and abroad, though progress updates and publicly available information are less frequent.

One scenario that could adversely affect vaccine programs is further evolution and spread of viral variants resistant to vaccine-induced neutralizing antibodies. New viral variants are spreading rapidly and may have implications for the vaccine landscape. Due to multiple mutations/deletions in the genetic sequence there are concerns over potential impact on the effectiveness of current vaccines, monoclonal antibodies and diagnostics. There is an urgent need to anticipate further development of vaccines for the new variants, and for more stringent nonpharmaceutical interventions to maintain control (AMC Engagement Group, 2020). Fast-spreading variants have been detected in the United Kingdom (B.1.1.7), South Africa (B.1.351), Brazil (B.1.1.248 or P.1) and elsewhere, and are now circulating.

Two categories of variants have different implications for vaccine efficacy. The first category involves variants that arise from SARS-CoV-2 replicating in people. One selection pressure on the virus is to infect human cells more efficiently and maximize the replication of its genome, becoming a more transmissible virus that will spread more rapidly. This happened during (northern) spring 2020 when the D614G variant became the dominant strain globally. The same thing is happening now with the B.1.1.7 strain first detected in the UK. As of February 15, 2021, B.1.1.7 comprises roughly 95% of new SARS-CoV-2 infections in England, and has now been identified in at least 82 countries ([O'Toole et. Al., 2021](#)). The UK strain is more infectious and is projected to soon dominate the US pandemic as well. But neither the D614G variant nor the B.1.1.7 strain is notably resistant to vaccine-induced neutralizing antibodies, and most researchers have substantial confidence that these variants will not affect the efficacy of the present generation of vaccines ([Garcia-Beltran et. Al., 2021](#)).

The second category involves variants that are more concerning, represented by the B.1.351 and P.1 lineages that emerged in South Africa and Brazil, respectively. These viruses have sequence changes in key positions suggesting that they arose under neutralizing antibody selection pressure within people infected or previously infected with SARS-CoV-2. Unusual variants have been seen when the virus replicates at high levels for prolonged periods in immunocompromised individuals ([Kemp et. Al., 2021](#)).

Table 1 provides a summary of what we know about the variants and how they respond to various key vaccines. The disparate results serve as a warning flag that the world needs to step up its current vaccination campaigns and speed efforts to envision what COVID-19 vaccines 2.0 might look like.

Table 1: Main vaccines and their efficacy against variants

Vaccine (Company)	Preexisting Variants			Neutralization by Pseudovirion or Live Viral Plaque Assay			Efficacy in Settings with 501Y.V2 Variant
	Sample Size	Efficacy in Preventing Clinical Covid-19	Efficacy in Preventing Severe Covid-19	B.1.1.7 Variant	P.1 Variant	501Y.V2 Variant	
	no.	% (no. of events with vaccine vs. placebo)					%
Ad26.COV2.S (Johnson & Johnson)	43,783	66 (NA)	85 (NA)	NA	NA	NA	57†, 85‡
BNT162b2 (Pfizer)	34,922	95 (8 vs. 162)	90 (1 vs. 9)	Decrease by 2x	Decrease by 6.7x	Decrease by ≤6.5x	NA
mRNA-1273 (Moderna)	28,207	94 (11 vs. 185)	100 (0 vs. 30)	Decrease by 1.8x	Decrease by 4.5x	Decrease by ≤8.6x	NA
Sputnik V (Gamaleya)	19,866	92 (16 vs. 62)	100 (0 vs. 20)	NA	NA	NA	NA
AZD1222 (AstraZeneca)	17,177	67 (84 vs. 248)	100 (0 vs. 3)	NA	NA	Decrease by ≤86x to complete immune escape	22§
NVX-CoV2373 (Novavax)	15,000	89 (6 vs. 56)	100 (0 vs. 1)	Decrease by 1.8x	NA	NA	49§
CoronaVac (Sinovac)¶							
Brazil	12,396	51 (NA)	100 (NA)	NA	NA	NA	NA
Turkey	7,371	91 (3 vs. 26)	NA	NA	NA	NA	NA
BBIBP-CorV (Sinopharm)	NA	79 (NA)	NA	NA	NA	Decrease by 1.6x	NA

* Data were available up to March 18, 2021. The definitions of mild, moderate, and severe coronavirus disease 2019 (Covid-19) vary across the vaccine trials. A list of references associated with these vaccines is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. NA denotes not available, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† Shown is the efficacy of the vaccine, as compared with placebo, against moderate-to-severe Covid-19.

‡ Shown is efficacy of the vaccine, as compared with placebo, against severe Covid-19 and hospitalization.

§ Shown is efficacy of the vaccine, as compared with placebo, against symptomatic Covid-19.

¶ Data are shown separately for the trial sites in Brazil and Turkey.

Source: Karim & Oliviera, 2021 ([NEJM](#))

(2) Procurement agreements – serious equity challenges

Overall picture

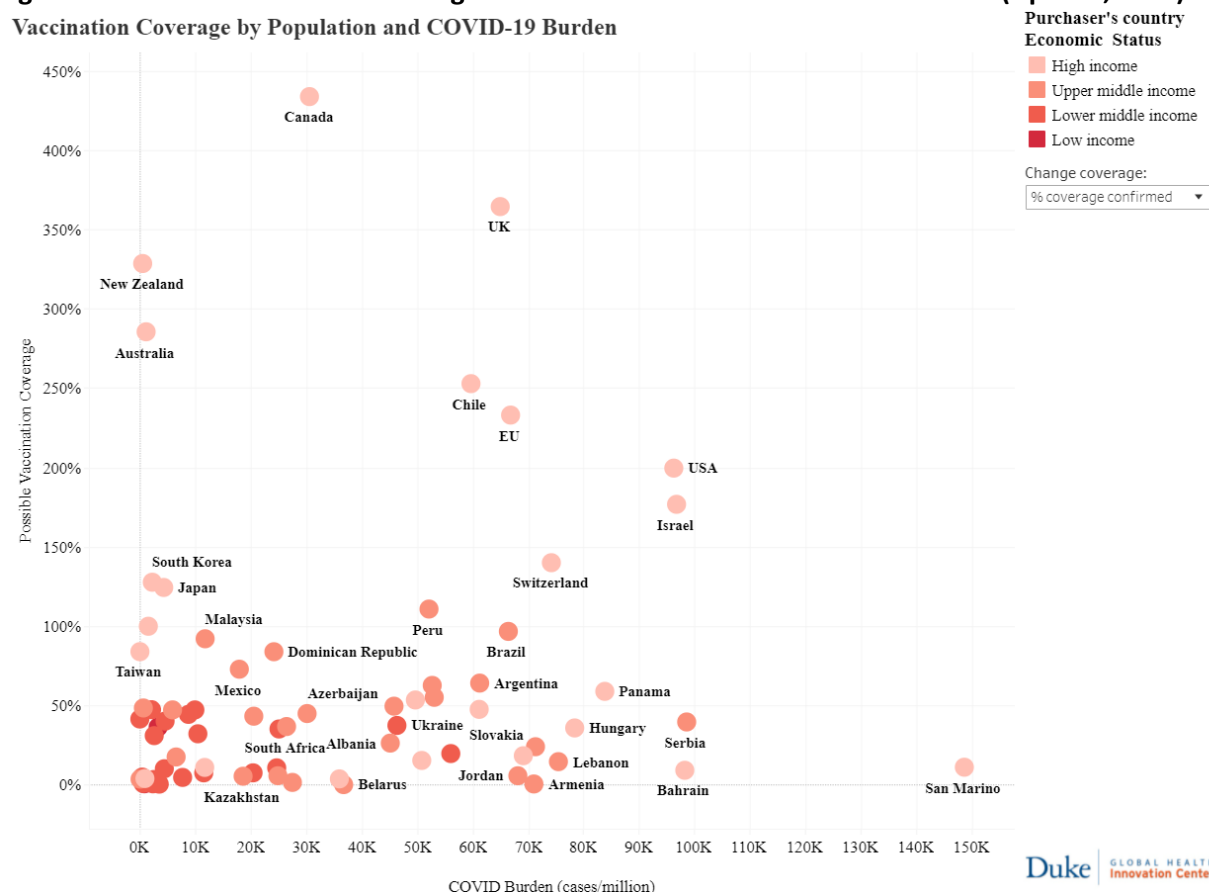
The key challenge with current vaccine agreements is inequity in access. Figure 3 suggests the failings of the current systems and a need for doing things differently. It shows high income countries – Canada, UK, Australia, New Zealand, Chile, in the EU, and US – secured more than 200% worth of vaccine doses (taking into account how many doses are needed per person for each vaccine, to show real potential coverage). Many others including all low-income countries are struggling with less than 50% potential coverage.

COVAX

To date COVAX has secured 2.07 billion doses. It is on track to deliver at least 2 billion doses by the end of 2021. According to the most recent COVAX forecasting, it expects as many as ~1.8 billion doses to be available to 92 low- and middle-income countries through its advanced market commitment (AMC). If this happens—which is a big if, with uncertainties around vaccines efficacy and safety, funding, capacity and country readiness – it means COVAX can reach at least 27% of the population of LICs around the world in 2021 ([GAVI, 2021](#)). This is significant progress for COVAX, but it is clearly insufficient for reaching herd immunity in low- and middle-income countries.

More information related to access, including insights on manufacturing capacity, price points, doses administered to date, etc. can be found in the following sections of the report.

Figure 3: Possible vaccination coverage based on secured doses vs. COVID burden (April 23, 2021)



Source: Lunch & Scale Speedometer (<https://launchandscalefaster.org/COVID-19>)

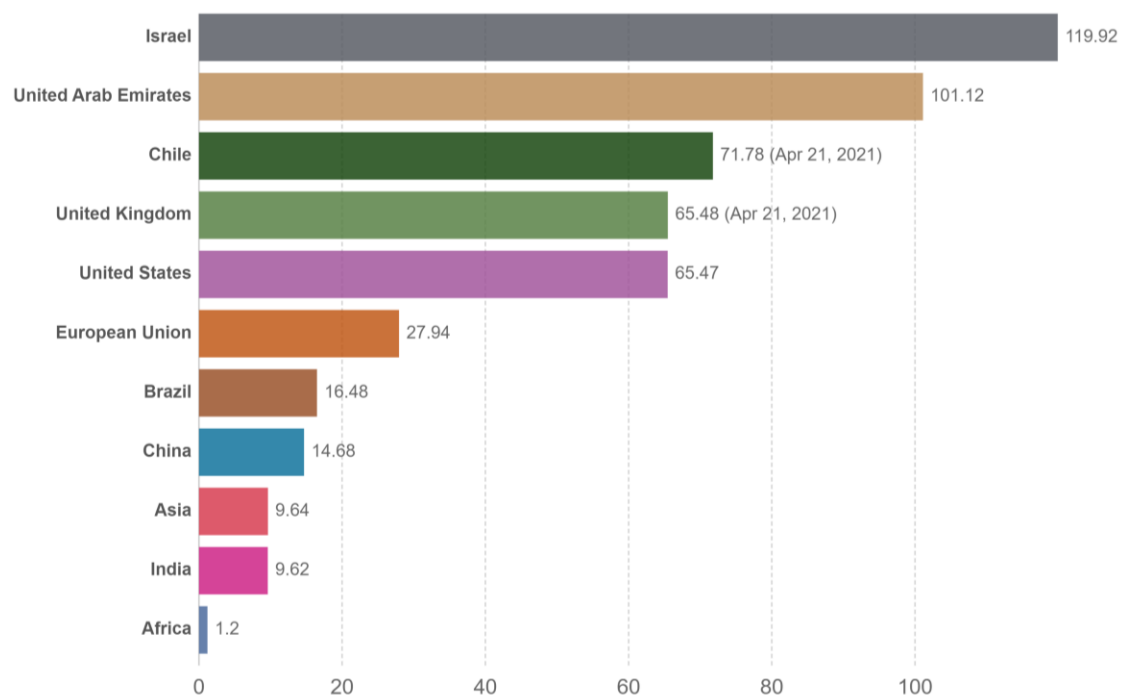
(3) Delivery – further reflection of equity challenge

With the start of the global vaccination campaign, countries experienced unequal access to vaccines and varying degrees of efficiency in getting people inoculated. Israel's immunization rates are the highest in the world (Figure 4), with more than 100 doses administered per 100 people (the doses are counted as a single dose, and may not equate to the total number of people vaccinated, depending on the dose regime). In contrast, Africa region has on average only 0.41 doses administered per 100 people to date.

As of April 23rd, more than 973.38 million doses of COVID-19 vaccine had been administered, with 15.62 million doses per day in the world ([Our world in data, 2021](#)). At the current pace it would take years to gain a significant level of global immunity. But the rate is steadily increasing and new vaccines from additional manufacturers will soon be available. Delivering billions of vaccines to stop the spread of COVID-19 worldwide will be one of the greatest logistical challenges ever undertaken. More related insights, for example on delivery readiness, can be found in the Delivery section.

Figure 4: Cumulative COVID-19 vaccine doses administered per 100 people per day as of Apr 23, 2021
(in selected countries/regions, not exhaustive)

Total number of vaccination doses administered per 100 people in the total population. This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).



Source: [Our world in Data](#)

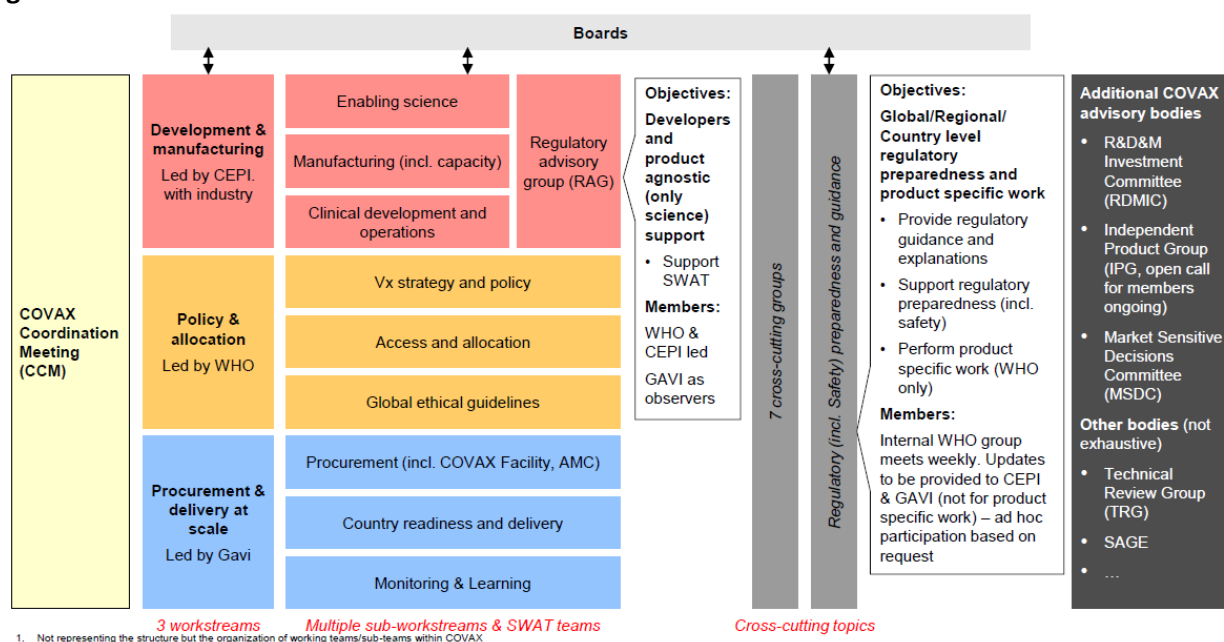
2. Analysis of successes, challenges, and lessons learned

(1) Governance & Coordination

What's Worked So Far

The main governance and coordination mechanism for COVID-19 vaccines is COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-A). The ACT-A has been referred to as “the only international effort that allows us to speak in one voice and raise funding for new tools.” It aims to provide a mechanism for: (i) end-to-end solutions from R&D to procurement and delivery; (ii) an integrated view of health systems and three key tools (i.e., vaccines, therapeutics, and diagnostics); and (iii) finding a global solution to a global problem seen from an equity perspective. The COVAX consists of 3 workstreams as well as multiple sub-workstreams and SWAT teams. It also has cross-cutting working groups led and represented by relevant institutions (Figure 5).

Figure 5: Overview of COVAX structure



Source: WHO

COVAX has been demonstrating unprecedented collaboration among key institutions such as CEPI, Gavi, and WHO. It brought together countries that can afford to self-finance vaccines (99 countries so far) and low- and middle-income countries (92 countries so far) that will be funded mainly through official development assistance (ODA), to mobilize billions of dollars. It also brought end-to-end functions together, leveraging strengths of each institution and empowering specialized agencies (e.g., CEPI, Gavi, WHO). WHO's role in COVAX has been limited to regulation, scientific norms and guidance, as well as allocation formula, etc. This is felt by many of the interviewees to be appropriate. Many attribute the strengths of COVAX to existence of reliable leading institutions for R&D (CEPI) and procurement and delivery (Gavi).

Challenges

While COVAX provides a solid foundation, the current coordination and decision-making mechanism faces strong criticisms from countries and CSOs. Key elements that the future system needs to address emerge from interviews and the Roundtable:

Greater inclusiveness and country consensus: The current system is seen by Low- and middle-income countries, major vaccine producing countries (e.g., China, Russia), and CSO groups as supply-driven, biased toward Western interests (and against China and Russia) and not inclusive.

Critical players such as Russia, China, and India have been less engaged in COVAX. This significantly limits its scope as a “global mechanism”. Many interviewees mentioned the absence of the United States, which used to lead such global efforts, as a major challenge (the new Biden administration announced its plan to join COVAX).

Funding Requirements: Experts interviewed noted that the world significantly underestimated the difficulties of financing vaccines. This was applicable at multiple stages of the vaccine value-chain, including: ignition funding, capital to start manufacturing at risk, for ensuring equitable access, and for post-pandemic period management of COVID as an endemic disease (e.g., long-term vaccine production considering immunity to the vector, mutations, etc.). Funding limitations hurt the ability to effectively incentivize and make deals with leading pharma companies to achieve equity. Overall lack of financing is one of the key challenges noted by Vaccine Roundtable participants and by several experts in interviews.

As a result institutional leaders spent a substantial amount of time on fund-raising activities at moments when more strategic discussions across the value chain were needed. Since COVAX did not exist at the beginning of the pandemic, funding came too late to secure a substantial portion of vaccines for low- and middle-income countries even given the rapid actions by CEPI at the beginning of the outbreak (See details in the R&D section). Pivoting to a narrative that the funding should come from outside official development assistance, given the significant economic consequences, also came too late. COVAX currently estimates a need to raise an additional US\$ 6.8 billion in 2021. While the AMC has met its urgent 2020 fundraising target of USD \$2 billion (raised USD \$2.4B), at least USD \$4.6 billion more is needed this year to procure doses of successful candidates as they come through the portfolio ([GAVI, 2020](#)).

Recent studies make a clear economic case for wealthier countries financing equitable global vaccination. The National Bureau of Economic Research in the US estimates that total global losses arising from inequitable distribution of vaccines can be \$1.8 to 3.8 trillion. Advanced economies may bear somewhere from 13 to 49 percent of these global losses. Depending on the different scenarios, this range corresponds to 0.3 to 3.7 percent of their 2019 GDPs ([Çakmaklı, et al., 2021](#)). Eurasia Group also estimates that the economic benefits of an equitable vaccine solution accrued by ten donor countries alone (US, UK, Germany, Japan, France, Canada, Qatar, South Korea, Sweden, and UAE) would be at least \$153 billion in 2020-21. Over the next five years, this sum rises to a cumulative \$466 billion, more than 12 times the \$38 billion total estimated cost of the entire Act-A program ([Eurasia Group, 2020](#)). A system would be required to enable wealthy economies to respond to this clear economic case and prepare for future pandemics.

Lessons Learned

- The future system needs to be more demand-driven, with broader participation and decision-making by countries and CSOs. It should address perceived biases toward Western interests.
- Active involvement of China, Russia, India, and the United States in a future coordination mechanism will be essential to make a truly global platform for vaccines solutions.
- Having a mechanism to secure quantum funding for vaccines in peace time before future pandemics is one of the most important issues.

(2) Research and Development (R&D)

What Worked So Far

Unprecedented Science:

Figure 6 provides details of clinical trials and status of use for each vaccine candidate after about 12 months in development.

Figure 6: Status of clinical trial and use for each vaccine candidate



Source: [LSHTM Vaccine Tracker](https://www.lshtm.ac.uk/vaccine-tracker)

As described earlier, conventional vaccine development averages 8-10 years between drug discovery and licensure. Clinical development alone usually runs between 2-10 years, with the process prolonged by lengthy and sequential review and approval processes (Lurie, 2020). Amongst the fastest previous vaccine projects are Merck's mumps vaccine [4.5 years in development (1963–67)] (Conniff, 2013) and the Ebola vaccine developed by Canada and licensed to Merck [5 years to licensure] (GAVI, 2020).

COVID-19 vaccines came to market faster at record speed (Figure 7). They did so because of crucial international scientific collaboration (Figure 7), as well as unprecedented amount of R&D funding (Figure

ensure equitable access. This included investment in a rapid response platform for MERS, another coronavirus. CEPI could quickly redirect partners when they learned of a new coronavirus of concern in January 2020. The mRNA vaccine platform developed for MERS (and SARS) by the Vaccine Research Center at NIH was rapidly mobilized for SARS-CoV-2. This was enabled by rapid funding from Biomedical Advanced Research and Development Authority (BARDA) and CEPI to biotech companies working on mRNA vaccines and other platforms to prepare CoV-2 candidate vaccines (Lurie, 2020).

As early as January 20, 2020 when there were less than 600 COVID-19 cases around the world—using an available \$100 million—CEPI made a simplified contract with Moderna and Oxford University to get their candidates to phase 1 clinical trial (payment to manufacturing lot for phase 1 trial). Contracts for other candidates followed a week later. This allowed CEPI to secure access commitments from these manufacturers before much larger bilateral funds came in. Most vaccines in development do not progress through to licensure, which is why CEPI invested in a broad portfolio of 11 COVID-19 vaccine candidates to maximize chances of success. Through this portfolio approach CEPI could support the development of multiple vaccines for distribution through COVAX, including the vaccines from Moderna and Astra Zeneca/Oxford.

Operation Warp Speed (OWS): A massive amount of funding for COVID-19 vaccine R&D, manufacturing, and purchasing has been supported by OWS of the United States. Specific targets of OWS include supporting R&D efforts from pharmaceutical companies for seven different vaccine candidates as well as various therapeutic compounds. It supported rapid scale-up of manufacturing capacity and organization and facilitation of simultaneous FDA review of Phase I-III clinical trials on the most promising candidates ([HHS, 2020](#)). OWS uses BARDA as the financial interface between the U.S. federal government and the biomedical industry ([Gorenstein, 2014](#)). The program was initially funded with \$10 billion ([HHS, 2020](#)), with additional funds allocated through BARDA. This increased to about \$18 billion by October 2020 ([Baker & Koons, 2020](#)). The Public Health and Social Services Emergency Fund (PHSSEF), the parent account for BARDA, has up to roughly \$30 billion (accounting for set-asides and transfers) that is *available* for vaccine development, manufacturing, and purchase until September 30, 2024 ([CRS, 2021](#)). These funds are also designated for other emergency response activities, such as medical supply procurement for the Strategic National Stockpile, supporting health care surge response, and the development, purchase, and manufacturing of therapeutics and diagnostics. Companies receiving R&D funds included J&J (Janssen), Astra Zeneca/ Oxford, Moderna, Novavax, Merck/IAVI (project terminated on Jan 25, 2021), and Sanofi/GSK.

Challenges

Funding Requirements: The above Vaccine Governance and Coordination section above described in detail the overall funding challenge for global vaccine efforts. This fully applies to CEPI which stretched itself to finance urgent R&D efforts as well as manufacturing at risk.

R&D collaboration & data sharing: Respondents noted that there are ecosystem gaps in getting virus samples, curating genetic sequences, and developing animal models. As an example, some have highlighted full information exchange with China and coordination for vaccine development for COVID-19 as having been problematic and in need of resolution (Lurie, 2020). Across the whole of the ecosystem there is a lack of data sharing rules (e.g., non-transparent clinical trial results). There is a need for better and more formal systems for sharing and collaborating in R&D. Sorting this out will be important for future preparedness and response.

Slow scientific review process: Given that some low- and middle-income countries have gaps in their capacities in robust scientific review processes, many rely on scientific validation and approval by WHO. This enables the vaccines to be financed through COVAX and the World Bank's \$12 billion funding. Some interviewees suggest faster review process by WHO would be important for significantly scaling the global distribution of vaccines.

Unclear vaccination strategy/technical product profile (TPP) linking R&D to delivery: A few interviewees and Roundtable participants commented that the world failed to lead the R&D process and product development using clear strategy and TPP guiding vaccines fit for global distribution and delivery. Lack of such efforts led to a situation where products requiring ultra-cold storage requirements (-60°C to -80°C) received more funding because they became available first. Also, clinical trials were designed to receive EUA as fast as possible rather than answering key questions related to vaccine efficacy, ease of administration, and safety. There is underlying incentive for wealthy economies with capacity to meet such ultra-cold storage requirements to support the vaccines that can come faster. This affects the availability of upfront funding – if COVAX existed with significant funding it may have been able to counter such incentives and drive R&D toward more equitable vaccine products.

Lessons Learned

- **Significant upfront financing for CEPI/COVAX-type mechanisms: any future pandemic should be met by massive, upfront, public sector funding to accelerate R&D and secure vaccine doses for equitable distribution.**
- **End-to-end lens and coordination for R&D: COVID-19 exposed several key gaps and issues in the R&D ecosystem. End-to-end coordination and strategic responses to such gaps in peace time is key to speeding time from pathogen characterisation to emergency use authorization for vaccines.**
- **Importance of continued investment in Science: The speed with which COVID-19 vaccines have been developed was due to a variety of factors and approaches carried out prior to the pandemic. This includes investments in science: platform technologies (as with mRNA), genome sequence sharing mechanisms, health systems, etc. Such investments need to continue or accelerate.**
- **Shortening the interval between vaccine doses – When people are infected after the first dose but before the second dose, the virus can replicate in the setting of a suboptimal level of neutralizing antibodies, a situation where resistant variants may emerge ([Saad-Roy, 2021](#)). The intersection between virus replication and host antibodies underpins the current recommendation of a short interval between vaccine doses, which, for example, is national policy in the US but not in the UK. The sooner each person receives the stronger protection conferred by the second vaccine dose the better both for individuals and for the population ([Moore, 2021](#)).**

(3) Manufacturing at Scale

What Worked So Far

Significant but highly variable manufacturing capacity: In many cases, manufacturing is yet to reach full scale. Manufacturing productivity will be influenced by multiple factors, which will in turn influence volume and timing of supply (COVAX, 2021). The reported global vaccine production volumes in 2021 could add up to 14 billion doses ([UNICEF, 2021](#)). This figure provides a highly optimistic view: it assumes all vaccine candidates at various stages of R&D will be successful, funded and produced as planned. The world has seen many vaccine developers walk back manufacturing projections over the past 4 months, with more production delays likely in the coming year. Current manufacturing capacity, based on publicly available data ([Knowledge Ecology International, 2021](#); [Third World Network, 2021](#)), is focused in a few regions (Europe, US, China, Russia, India, etc.) with very limited capacity in Africa and Latin America. This makes it difficult for these regions to access new vaccines.

CEPI: With the inevitability of vaccine demand outstripping supply in the short-term, CEPI stepped-up to address manufacturing challenges through strategic investments. Typically, CEPI does not pay for manufacturing/production. However, no other international institution has mandate and financing for this function, and preparations need to happen in parallel to the clinical trials. CEPI ended up putting approximately USD \$600-700 million to get this ball rolling, and had to borrow from core funding to keep activities going. This expansion into manufacturing enabled at-risk volume guarantees tied to R&D investments with priority access for low- and middle-income countries. CEPI is expanding the global manufacturing network for its vaccine portfolio. Biofabri (Spain) and GC Pharma (Republic of Korea) will reserve vaccine manufacturing capacity for more than 1 billion doses of COVID-19 vaccines by agreement with CEPI. This capacity will go towards the COVAX goal of producing at least 2 billion doses by the end of 2021.

Serum Institute of India: Over a billion of COVAX's doses are likely to be produced by the SII, the world's largest vaccine manufacturer by volume, at a cost of no more than US\$ 3 per dose. This is the product of a [unique collaboration](#) set up last (northern) summer between Gavi, the Bill & Melinda Gates Foundation and SII, which funded an expansion of manufacturing capacity at SII's India headquarters. ([GAVI, 2021](#)) This partnership has been touted as manufacturing for the Global South by the Global South. The SII is also to provide almost all of India's vaccines in addition to 1 billion doses of AstraZeneca/Oxford vaccine. SII is producing a vaccine using the Oxford-AstraZeneca formula for India and other developing countries.

Competitor collaborations: Manufacturing collaborations between industry competitors is also happening. For example, Sanofi stepped up to help produce 100 million doses of Pfizer/BioNTech coronavirus vaccines in Europe ([Nathan-Kaziz, 2021](#)). Following the announcement from Sanofi, Novartis is also now exploring whether it can deploy its own manufacturing network to boost COVID-19 supplies ([Saganowski, 2021](#)). To enhance such collaborations, the United States is weighing the Defense Production Act to compel drug makers to produce more Pfizer or Moderna vaccines ([Spalding, 2021](#)).

Manufacturing as a means to access:

With less purchasing power for early access to vaccine doses, MICs are using other strategies to get to the front of the queue. Countries with manufacturing capacity, such as India and Brazil, have been successful in negotiating large vaccine deals with leading vaccine candidates as part of the

manufacturing agreements. For countries without manufacturing capacity, those with the infrastructure to host clinical trials, such as Peru, have used that as leverage to negotiate purchase deals.

Challenges

Artificial significant scarcity: Several times as many doses as the 20% floor set by COVAX will likely be needed. Demand will increase if vaccines provide limited immunity and require regular booster shots (Frederiksen et. al., 2020). Based on this estimate, ~5.3 billion vaccine doses are required for a single-dose vaccine, or possibly 12–16 billion in case of a multi-dose vaccine. As COVID-19 becomes endemic, the world may require vaccines every year or more frequently: it is becoming clear that this will not be a single event.

COVAX is currently only “encouraging” manufacturers to share technology and scale-up supply among a limited pool of suppliers. It justifies the voluntary approach based on the complex nature of technology transfer (Rizvi, 2020). But limited sharing dictated by market access considerations could fail to make full use of all available global production capacity. This could in turn lead to artificial scarcity.

Intellectual Property Rights (IPR) & global common goods: Manufacturing constraints and resulting inequity precipitated considerable global conversation about systems for establishing global public goods and how IPR could be shared. One potential related watershed is a proposal by India and South Africa to the World Trade Organization (WTO): it would allow all countries to choose to neither grant nor enforce patents and other intellectual property (IP) related to COVID-19 drugs, vaccines, diagnostics and other technologies, including masks and ventilators, for the duration of the pandemic, until global herd immunity is achieved. The proposal requests a waiver be granted to WTO members so that they do not have to implement, apply or enforce certain obligations related to COVID-19 products and technologies under Section 1 (copyrights and related rights), 4 (industrial design), 5 (patents) and 7 (protection of undisclosed information) of [Part II of the TRIPS Agreement](#). This would provide countries with the space to collaborate in R&D, manufacturing, scaling up, and supplying COVID-19 tools.

The proposal has received strong global support from civil society, international organizations (UNITAID, UNAIDS, WHO), academics and a majority of developing countries, including China. It has been opposed by high-income countries including at the time of writing the United Kingdom, United States, Canada, countries in the European Union, Switzerland, Australia, Japan and even Brazil. The TRIPS Council is holding a number of informal meetings to address issues raised. The main arguments against the waiver are that the scope is too broad and uncertain; that current options within the TRIPS agreement are sufficient, that IP has helped drive COVID innovation; that companies are doing voluntary licencing, that COVAX is there for this purpose, and that IP is not a barrier. The arguments further claim the main challenges are in distribution, health system readiness, capacity, etc. For the argument that IP has helped drive COVID innovation, there is a counterargument that the massive amount of public funding should have been sufficient for companies to drive COVID innovation.

It was also noted that WHO’s voluntary COVID-19 Technology Access Pool (C-TAP) would have been a place where IP could be shared, but was a missed opportunity. C-TAP was created as an option to compile, in one place, pledges of commitments to voluntarily share COVID-19 health tech related to COVID-19 knowledge, IP and data. The pool was endorsed by 40 countries but most with major R&D and manufacturing capacity are absent.

Regulatory, liability and indemnification: All vaccines made available or procured through COVAX will have received regulatory approval or an EUA allowing for their general availability. But even under normal circumstances vaccines approved for general use may, in rare cases, cause unexpected serious adverse events (SAEs). Those involved in their manufacturing, distribution and administration are normally insured to cover this risk. Given the unprecedented nature and scale of the pandemic, normal insurance will not be available from the outset. The lack of such coverage may limit or delay global access to vaccines. Manufacturers may be reluctant to deliver if the risk is not addressed. Regardless, they are also looking to countries receiving and deploying vaccines – including via bilateral deals – to indemnify them against product liability claims (as was the case during the H1N1 pandemic). People receiving vaccines who suffer unexpected SAEs associated with a vaccine or its administration are generally entitled compensation. These issues became important for low- and middle-income countries. COVAX is developing standardized regulatory solution to indemnity, as well as a system to provide compensation to individuals in the 92 economies under the COVAX AMC ([COVAX, 2020](#)).

Raw materials constraints in scaling production – Logistical, contractual, and even diplomatic challenges requiring new forms of collaboration have been cited by McKinsey with regard to raw material constraints to manufacturing. While there is sufficient global manufacturing capacity for syringes and fill-finish materials, suppliers of many niche chemical and biological vaccine components are scattered, with countries competing for limited resources. Many vaccine manufacturers have sought highly specialized contracts with manufacturing partners (e.g., mRNA loading into lipid nanoparticles under strict regulations; Moderna with Catalent and Lonza).

Quality-assurance challenges in manufacturing – Strong quality assurance systems are required for new classes of vaccines (e.g., mRNA or viral vectors) at unprecedented scale. Well-established regulatory authorities (e.g., FDA) continue to develop standards. The ability to stay apprised of requirements can be challenging. Add to this the use of contract manufacturing and tech transfers and it becomes more complex to ensure quality control. Currently, with the exception of India and perhaps a few others, manufacturing capacity is geographically concentrated, with disproportionately low capacity in low- and middle-income countries. There is limited current capacity to manufacture new mRNA vaccines regardless of income level.

Leadership and financing of at-risk manufacturing at scale were cited as key challenges. Central stakeholders such as CEPI (focus on R&D) and GAVI (focus on procurement and delivery) do not have mandates in this area. Identification of who is best placed to fill this gap is required, with greater clarity for roles. There is also a need for substantial international funding and coordination. India, for example, noted that there were no global provisions for this, and had to self-finance to meet global demand.

Lessons Learned

- **Funding:** Major funding efforts are needed to strengthen and support manufacturing capacity (e.g., India had to self-finance). Financing is at the core of the failure to secure enough doses for global access. This could be assisted through the strengthening and maintenance of capacity in peace time.
- **Global architecture for manufacturing at risk is lacking:** COVID showed the need for a global pandemic manufacturing solution, underpinned by strong leadership and coordination. This leaves a critical gap. There is a need for clarity on who will be responsible for it, followed by substantial funding.

- **Measures to ensure a Global Health Commons:** There is a need for a wider discussion around options to ensure access to vaccines as a Global Health Commons during pandemics. Building consensus around IPR, C-TAP, TPP, and liability and indemnification in parallel to addressing the financing issue for COVAX would be critical for future pandemics.
- **Partnership with major manufacturing countries:** In addition to India, partnerships with other major manufacturing nations such as China and Russia could help. A transparent mapping exercise of such capacity, as well as that of raw materials suppliers would be beneficial, with some initial attempts being made (e.g. [Vaxmap](#)).

(4) Procurement

What Worked So Far

COVAX and its Advanced Market Commitment: Figure 10 provides details of the recent COVAX forecasting that expects to procure over two billion doses in 2021, of which ~1.8 billion doses are for 92 low- and middle-income countries through AMC (~28% coverage of AMC populations). The breakdown of the five procurement deals it signed is as follows:

- **Deal with SII to provide doses for AMC92 economies**
 - SII / AstraZeneca collaboration announced on Aug 7, 2020
 - SII / Novavax collaboration announced on Sep 29, 2020
- Deal with AstraZeneca announced on Dec 17, 2020
- Deal with Pfizer / BioNTech announced on Jan. 22, 2021
- MoU with Janssen / J&J announced on Dec 17, 2020
- Statement of Intent with Sanofi / GSK, announced on October 28, 2020

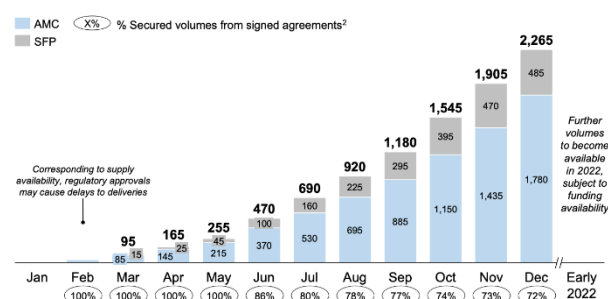
Figure 9: COVAX Global Supply Forecast by AMC-Eligible and Self-Financing Participants + Candidate Specific Supply

COVAX Facility global supply forecast by AMC-eligible and SFP

AS PER 2021-03-02

PRELIMINARY AND SUBJECT TO ASSUMPTIONS

COVAX Available Supply, Cumulative, Mn doses, 2021¹



¹ Supply refers to volumes of vaccine available from the manufacturer. Timing of forecasts is based on anticipated release of doses from manufacturers. Volumes for expected single-dose regimen vaccine candidates doubled to ensure comparability across vaccine candidates. Volumes have been rounded to the nearest 5M (except for those smaller than 5M), and so totals may not equal sum of segments.

² Signed agreements include legally-binding agreements, memoranda of understanding, and statements of intent.

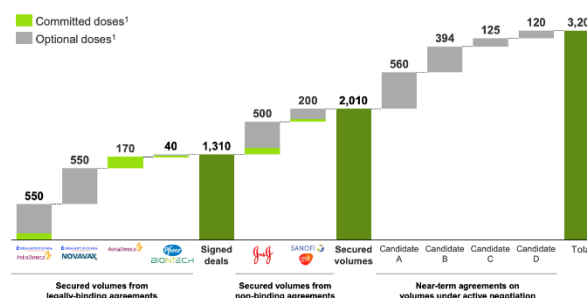
COVAX Facility candidate-specific supply

2021 and 2022

AS PER 2021-03-02

PRELIMINARY

COVAX Available Supply, Mn doses, 2021 and 2022



¹ "Committed doses" are doses that the COVAX Facility is required to purchase once a legally-binding agreement has been signed. "Optional doses" are doses that the COVAX Facility has the option to make a firm order commitment for in the future, but is not required to purchase. Note: Building on the recently announced memorandum of understanding with Novavax, negotiations on the final terms of the agreement and the distribution of volumes between Novavax and the Serum Institute of India are ongoing; updates will be published in due course.

To address significant shortage of COVAX supplies from acquiring herd immunity, countries are procuring and actively in discussion bilaterally with vaccine producers, including China, Russia and India:

- **China has 5 vaccine candidates in the final stages of trials which have taken place in at least 16 countries. In exchange, many of these host countries have been promised early access to the successful vaccines -- and in some cases, loans and the technology know-how to manufacture**

them locally. China currently has capacity and funding to manufacture 1 billion doses/year and can expand further. Based on Vaccines Roundtable, China appears to value COVAX, but sees critical need for the future global system to build full consensus among countries.

C.

- China reports that it has offered vaccine assistance to 53 developing countries, and that it has exported or is exporting vaccines to 22 nations. Since January 2021 CoronaVac, for example, has won approval for emergency use in countries such as Indonesia, Turkey, Brazil and Argentina. Sinopharm's China National Biotech Group will also supply 10 million doses of COVID-19 vaccines to COVAX. More than 10 million doses of the vaccines have been administered overseas since the end of last year (China Daily, 2021). It is on the African continent where the Chinese vaccines are being marketed the most intensively. Beijing has confirmed that it is assisting 21 African countries to get vaccines. Egypt, Africa's fourth largest country by population, has signed an agreement with China's Sinovac to produce its COVID vaccine, as well as distribute it to other African countries. 600,000 doses of Sinovac were also donated to the Philippines, and 3 million delivered to Indonesia along with the commitment to help Indonesia become a manufacturing hub for Chinese vaccines. China notes that it is providing vaccines to 14 Asian countries including Pakistan, Brunei, Nepal, the Philippines, Indonesia, Myanmar, Cambodia, Laos, Sri Lanka, Mongolia and the Palestinian Authority. China has also been active elsewhere in the Middle East region, supplying the UAE, Iran, Bahrain, Jordan, Iran, Egypt and Morocco. Early agreements were also signed with Mexico, Malaysia, Thailand, Chile, Hong Kong, and Ukraine.
- Russia has registered 2 vaccines, with Sputnik V vaccine being the first in the world to have been registered. Phase 3 trials are being planned/conducted in countries including Belarus, UAE, India, Venezuela, Egypt and Brazil. According to the Russian government, the vaccine demonstrated 91.6% efficacy based on data analysis of the final control point of clinical trials. Mass production is starting in other countries in partnership with local sovereign wealth funds, including Germany, India, South Korea and Brazil, as well as in China, Saudi Arabia and Turkey. The current manufacturing capacity is to immunize 500 million people per year (with 2 doses). Russian officials claim to have provisional orders from some 50 countries for 1.2 billion doses of Sputnik V and say they have negotiated deals with firms in South Korea, India, China, Kazakhstan and Hungary ([Morris et. al., Washington Post, Nov 2020](#)). Russia has been vocal that its vaccine efforts have been purposefully left out of multilateral efforts, including COVAX, although they would be willing to participate if there were fewer Western biases.
- Meanwhile, by 25 February 2021, Sputnik V had been registered in 37 countries, including many in Africa. South Africa's regulatory authority received an application for licensing from Gamaleya on February 24th and was in the process of considering safety, quality and efficacy of the vaccine. Although mostly limited to government officials, Guinea started to vaccinate people on an experimental basis with Sputnik V. Ghana also noted that it had registered Sputnik V in order to provide backup doses to those vaccine provided through COVAX. (China Daily, 2021) Russia has intensive efforts in vaccine markets in Eurasia and is also making inroads in the European Union (TASS, 2021). At least 10 Latin American countries have also received Sputnik V, starting with Argentina on 30 December. Since then Belize, Brazil, Bolivia, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay and Venezuela have all received doses – some as small donations and others as paid orders. Russia has also licensed manufacturing companies to produce its vaccine in India, Brazil, China, South Korea, and Argentina.

- WHO has repeatedly urged both Gamaleya and Sinopharm, as well as countries, to refrain from bilateral deals and procure their COVID-19 vaccines through the COVAX facility.
- India has donated 1.7 million doses to Myanmar, while also providing free vaccines to at least 15 countries, including in Africa, the Middle East, the Caribbean and more regionally (Bangladesh, Bhutan, Nepal, Myanmar, Mauritius and the Seychelles). As of the end of January 2021, India also sent two million doses to Brazil and plans on shipping more (Dyer, 2021). It has so far provided ~36 million doses to other countries, both free and on a commercial basis (JakartaPost, 2021).

Regional Procurement: Regions emerged during the pandemic as an important level from which to secure procurement deals. The African Union announced that it had secured 400 million doses for its members through its COVID-19 African Vaccine Acquisition Task Team (AVATT) (Nkengasong, 2021). This comes on top of an earlier announcement that it had secured 270 million doses. The [Africa Medical Supplies Platform](#) (AMSP), on behalf of the Africa Centres for Disease Control and Prevention (Africa CDC), recently launched its pre-order program for all Member States. Vaccines will include those from Pfizer, Johnson & Johnson and AstraZeneca/SII ([Africa CDC, 2021](#)). To support vaccination operations, AMSP has also launched a new category on vaccine accessories which will help Member States to procure products such as ultra-low temperature freezers, personal protective equipment, cotton wool rolls, syringes and needles. Financing is being provided through the Afreximbank financing facility, which builds on the success of its Pandemic Trade Impact Mitigation Facility. It is providing advance procurement commitment guarantees of up to US\$2 billion to candidate vaccine manufacturers ([Africa CDC, 2021](#)). Countries can pay back the loans in instalments over five to seven years using their own resources, World Bank funding or other resources. African Union Member States will pay between \$3 and \$10 per vaccine dose to access the vaccines procured through the AU ([Reuters, 2021](#)).

Challenges

Equity: As noted in the Overview section, the vaccine agreements to date reflect a picture of inequitable procurement. Unprecedented global need for vaccines bred competition for limited doses and manufacturing capacity. HICs have hedged their bets, purchasing enough doses to vaccinate their population several time over, while low- and middle-income countries are largely being left out ([Duke University, 2021](#)). The larger direct deals made by HICs (and some MICs) result in a smaller fraction of the pie remaining for equitable global allocation. This approach has resulted in the majority of vaccines going to HICs and fewer doses available for low- and middle-income countries and partnerships such as COVAX. Many people in low- and middle-income countries may have to wait until 2023 or 2024 for vaccination ([Launch & Scale Speedometer, 2021](#)). Manufacturers are [being encouraged to prioritize supply and rollout through COVAX](#), but there is no legal requirement to do so.

Pricing: The Analysis by So & Woo found that prices for vaccines have varied by more than 10-fold, from US\$6.00 (£4.50; €4.90) per course to as high as \$74 per course. ([So & Woo, 2020](#)). More recent analysis from UNICEF shows average price per dose ranging from US\$2.19 to \$44.00 ([UNICEF, 2021](#)). While attempts are being made to achieve more equitable pricing, some vaccines may be priced out of reach for some countries.

There are also instances of positive pricing trends. SII, for example, will provide 100 million doses of AstraZeneca's vaccine at \$3 each to AU, roughly what it said would be the price for India's government, and what has been noted as a ceiling price under COVAX AMC ([UNICEF, 2021](#)). That is enough to vaccinate 50 million people with its two-dose regimen. Pfizer will provide 50 million doses of its two-

shot vaccine at \$6.75 each. By comparison, the European Union and the United States are paying around \$19 per dose, while Israel is paying \$30 for the Pfizer vaccine. J&J will provide 120 million doses of its single-shot vaccine at \$10 each. The U.S. government is paying around \$14.50 a dose, including development costs. ([Reuters, 2021](#))

Lessons Learned

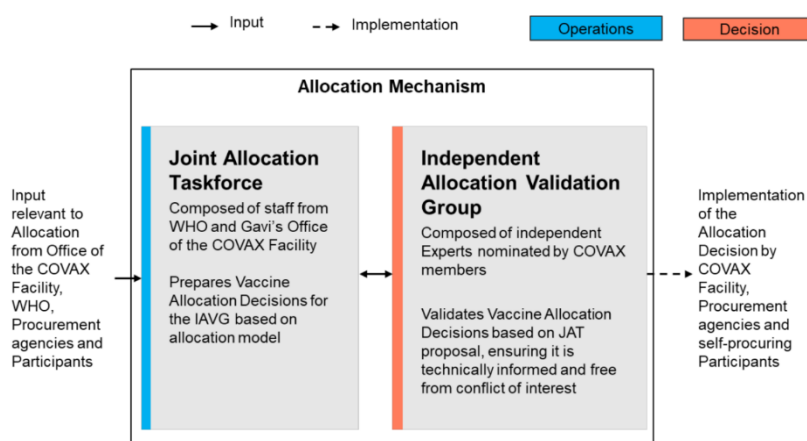
- **Improve procurement mechanisms through innovative financing mechanisms (e.g., iterations on AMC structure to create incentives for further investments) that provide sustainable and sufficient global health financing to procure sufficient doses based on demand. Continuity of pooling approaches, improved linkage of upstream investments and volume reservations will be required. Greater assurances of equitable distribution through greater transparency and accountability over these arrangements early on should become common practice.**
- **Strengthening of regional capacity to review vaccine candidates and negotiate with vaccine producers became important. Regions emerged to be important units for pooling of demand and funding, sharing of information, solidarity and country ownership. Strategic support to regional procurement initiatives may be an important role of the international system for future pandemics.**

(5) Allocation

What Worked So Far

COVAX recently published projected allocations by country through May. This was done by two new bodies established specifically to deal with allocation (Figure 10) – the Independent Allocation of Vaccine Group (IAVG) and the Joint Allocation Taskforce (JAT). Following the JAT's proposal on initial Pfizer vaccine distribution plans based on available volumes, readiness and rollout plans, the IAVG validated the plan for first wave participants. The COVAX then finalized and distributed the plan. All COVAX participants have now received information on indicative allocations plans for the AstraZeneca doses which started rolling out on Feb 24, 2021, with the first shipment to Ghana. Pfizer and AstraZeneca vaccines should be followed by other vaccines, including Novavax and Johnson and Johnson.

Figure 10: Allocation Governance Structure



South-East Asia is projected to receive 695 million doses through COVAX by the end of 2021, and WHO's AFRO region 540 million doses. This is followed by 355 million to the Eastern Mediterranean region, 280 million to the Americas and the Caribbean, 225 million to the Western Pacific region and 165 million to Europe ([GAVI, 2021](#)).

The [current allocation mechanism for COVAX has established two key phases:](#)

- **Phase 1: Proportional allocation up to 20% of pop.; receive doses proportionally to pop.; progressively receive doses until all countries reach 20%; rate of receipt depends on country readiness and the availability of doses (not on threat and vulnerability); moves to phase 2 once all countries have reached 20%.**
- **Phase 2: Weighted allocation beyond 20%; will depend on coverage % requested beyond the initial 20%; in case of severe supply constraints, countries will receive doses at variable rates, based on consideration of vulnerability and COVID-19 threat; those with higher risk would receive doses faster than others, although all countries will receive some doses in each allocation round; if no severe supply constraint, rate at which participants receive vaccines is such that all countries will achieve same coverage at same time (like phase 1); If a severe supply constraint, rate at which participants receive vaccines will be adjusted based on risk assessment (threat and vulnerability). For the vast majority of the signed deals for nearly two billion doses, COVAX has guaranteed access to a portion of the first wave of production, followed up at scale as further supply becomes available. This includes delivering at least 1.3 billion donor-funded doses of approved vaccines in 2021 to the 92 low- and middle-income economies eligible for the COVAX AMC. ([WHO, Dec 2020](#))**

Given that some populations will not be covered by the global allocation of vaccines, there is a risk of additional equity gaps. In particular, populations including refugees, internally displaced people, asylum seekers etc. may face additional vulnerabilities. In response a humanitarian buffer, representing 5% of the volumes supplied by COVAX (e.g., 100 million doses by end of 2021), has also been established along with a technical working group to further the details of these efforts.

Challenges

The 20% allocation of doses established as a floor by COVAX to cover the populations of the 92 AMC countries is considered by multiple stakeholders to be too low. While the intention was to secure enough doses to end the acute phase of the pandemic by ensuring health workers, the elderly and vulnerable groups are protected by the end of the year, it is well recognized that herd immunity could not be achieved at these levels of coverage.

Slow allocation and limited transparency: As discussed above, countries were generally passive recipients of information with regard to vaccine dose allocation. Some of the country representatives interviewed noted that their Ministries of Health were in the dark and, while not worried so much about whether doses would be secured, were more concerned about when they would arrive. The lack of communication early on led to countries seeking alternative supply arrangements outside of COVAX. One country respondent noted that this lack of information was also a challenge because Ministries of Health need to demonstrate to legislatures that they are on top of things. If they are perceived to have lost track or control of the process, particularly after funds have been committed (in the case of self-financing countries), this can be problematic and lead to hesitancy to engage.

Lessons Learned

- **Increase 20% floor: A higher coverage target should be established from the beginning, focused on achieving herd immunity.**
- **Communication and Data Transparency: Clear, consistent, frequent, honest, 2-way communication between countries and global organizations is critical in the absence of clear lines of sight to doses.**

(6) Delivery

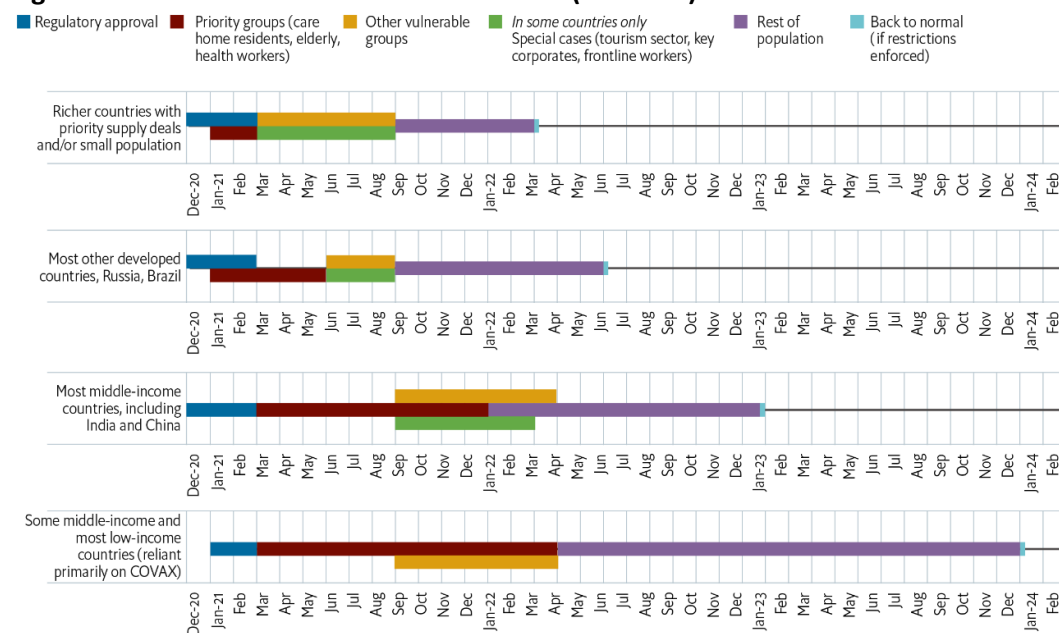
While it is still too early to draw any concrete conclusions delivery systems, this section provides some initial observations based on experiences to date.

What Worked So Far

Clear Priority Groups: Vaccine rollout through various phases has started in many parts of the world, mostly in HICs (Figure 11). In the EU for example, all 30 EU/EEA countries have started vaccinating the priority groups included in their first phase ([ECDC, 2021](#)). Some countries have already progressed to groups included in subsequent phases. In most low- and middle-income countries, distribution and implementation plans are still under development but generally align with similar guidance from WHO SAGE ([WHO, 2020](#)) for priority groups that will be covered by initial COVAX doses expected to start rolling out in February:

- **Priority 1: Those needed to control infection: frontline workers in healthcare, agriculture, social care, and security (countries differ by which categories are included in frontline workers).**
- **Priority 2: Those at highest risk of mortality: people with co-morbidities and people 65 years of age and older.**

Figure 11: Covid-19 Vaccines rollout schedule (estimate)



Accurate as at January 22nd, 2021
Source: The Economist Intelligence Unit.

Country readiness assessments and organized process under COVAX: WHO, UNICEF, Gavi and partners are working together to help prepare countries to be ready to introduce COVID-19 vaccines. Adaptable guidance, tools, trainings, and advocacy materials are being developed to support countries in preparing for COVID-19 vaccination with country plans having to fulfil four minimum criteria areas to proceed in

the allocation exercise: 1) target population, 2) supply chain management and logistics, 3) costing and funding, and 4) vaccine safety. Regional Review Committees will then:

- **Assess country preparedness across key areas of the National Deployment and Vaccination Plan (NDVP) and provide feedback to support country readiness**
- **Develop recommendations to highlight areas in need of further work or flag any potential technical assistance needs to support improvements in future iterations of the NDVP**
- **Confirm adequacy for the 92 AMC economies in the four areas considered to be the minimum criteria that must be met before countries can proceed in a global vaccine allocation exercise**
- **Verification of indemnity, liability, import procedures and regulatory aspects will take place prior to shipment orders being confirmed**

To complete critical readiness steps, COVAX has allocated funding for technical assistance to support the AMC-92 Participants. Until now, there has been inadequate and unequal investment in public health infrastructure and roll-out readiness. COVAX is also incorporating lessons learned from existing vaccination programmes and past emergency vaccine introductions including pandemic and seasonal influenza vaccination programmes, Ebola, polio, hepatitis, yellow fever, cholera, and meningitis.

COVAX Cost-sharing to achieve higher population coverage: Participants will now be able to cost-share, drawing on multilateral development bank funds to purchase additional doses. This will supplement the foundation provided by donors and achieve higher population coverage at US\$7/dose. Based on current supply estimates, at least 400M doses will likely be available in 2021 for COVAX to purchase via cost-sharing or further donor funds through AMC.

Regular forecasting: According to the recent COVAX forecasting and assuming funding availability, as many as ~1.8 billion doses are expected to be available to the 92 economies of the AMC in 2021, corresponding to ~28% coverage of AMC populations ([COVAX, 2021](#)). Requests for vaccines placed by Self-Financing Participants should be fulfilled in the second half of 2021. There are many uncertainties affecting the supply of COVID-19 vaccines in 2021, not least around manufacturing capacity, regulation, funding availability, final contract terms and the readiness of countries themselves to begin their national COVID-19 vaccination programmes ([COVAX, 2021](#)).

Early Challenges

Hesitancy/Skepticism: vaccine hesitancy and/or skepticism is emerging as a challenge affecting certain segments of all populations. This has been heavily influenced by what WHO termed an “infodemic”. An October 2020 study in *Nature Medicine* surveyed 19 countries and found that only 71.5% of respondents reported that they would be very or somewhat likely to take a COVID-19 vaccine, while 48.1% reported that they would accept their employer’s recommendation to do so. Differences in acceptance rates ranged from almost 90% (in China) to less than 55% (in Russia). Respondents reporting higher levels of trust in information from government sources were more likely to accept a vaccine and take their employer’s advice to do so. (Lazarus, 2020). In addition, although public health authorities and clinicians will recommend that people accept whatever approved vaccine is offered, media reports from the UK and Europe indicate that some people have resisted receiving the AstraZeneca vaccine and prefer the mRNA vaccines. Careful messaging will be important in such instances.

Distribution: In certain places the COVID-19-vaccine effort has hit a few speed bumps including accumulation of stockpile. Deployment to vulnerable countries and at-risk groups is slower than expected ([Mckinsey, 2020](#)). Through interviews with officials in India, Ethiopia, and Peru, Duke Global Health Innovation Centre researchers ([2021](#)) have also identified several critical challenges to distribution noted by country representatives:

- **Using childhood immunization infrastructure to target elderly populations;**
- **Cold-chain capacity, especially in rural and remote locations (requirements range from standard refrigeration to standard freezer to ultracold at -80°C);**
- **Needle supply and proper disposal of biohazard waste;**
- **Lack of trained providers to implement vaccines, particularly in rural areas;**
- **Accurate tracking of vaccinations, particularly for candidates requiring more than one dose;**
- **Mistrust and misinformation, particularly in dynamic political climates with upcoming national and sub-national elections.**

Early Lessons Learned

- **Distribution challenges need focused attention and investment now (or prior to pandemic):** More funding will be needed to ensure, for example, that cold-chain transport and storage, information systems, and trained providers are ready—particularly for last-mile areas. There is also growing concern that mistrust and misinformation about COVID-19 vaccines will prevent uptake.
- **Systems to monitor vaccination administration and coverage are needed.** Data collection and transparency is critical. Documentation regarding which vaccine product has been administered and when is key to the success of vaccination programmes. Such documentation is also important for monitoring any safety signals such as an adverse event following immunisation (AEFI) that may arise for any of the vaccine products, and for producing reliable estimates of vaccine effectiveness.
- **Design systems and policies that enable rapid introduction of vaccines and mobilization of surge capacity while preserving continuity of essential health services.** Extensive coordination between national and local authorities and multidisciplinary participation is required in planning and implementation of vaccination strategy.

CHAPTER 3 – IN-DEPTH REPORT ON THERAPEUTICS

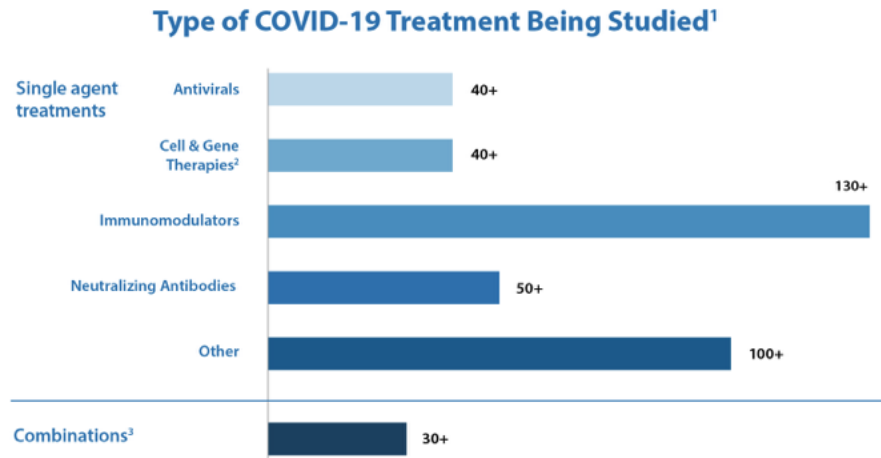
1. Overview of the current state

Researchers from around the world have been working at record speed to find ways to treat and prevent COVID-19. Thus far, results have been less than expected, with one key informant noting: “I wish I had more good news and more sound data to share at this point...but so far dexamethasone and oxygen therapy are really the best we’ve got.” Regimens with uncertain value are being used worldwide while being evaluated in clinical studies ([Harrington et al, 2021](#)).

From early 2020 through 2021, several hundred drug companies, biotechnology firms, university research groups, and health organizations had in development more than 600 potential therapies for COVID-19 disease in various stages of preclinical or clinical development ([BioWorld, 2021](#)), with approximately 411 therapeutic drug candidates in clinical trials as of March 9, 2021 ([BioRender, 2021](#)). Therapeutic drugs are any molecules used to diagnose, treat or prevent a disease. Unlike vaccines, therapeutic drugs directly affect the disease in question or modulate the immune system to help deal with the disease, but provide no form of ‘memory’ that would help the body fight off the disease at a future encounter. They can be composed of numerous entities including chemicals, proteins, or nucleic acids. ([BioRender, 2021](#))

From investigating the possibility of re-purposing existing drugs to searching for novel therapies against the virus, current approaches to COVID-19 therapies generally fall into one of five broad categories (or a combination of them), with immunomodulators seeing the most activity (Figure 12):

Figure 12: Types of Therapeutics Being Studied⁸



Source: [FDA, 2021](#)

- **Antivirals** - keep viruses from multiplying and are used to treat many viral infections (such as HIV, Herpes, Hepatitis C, and influenza); declining impact with disease progression; more effective early on.
- **Immunomodulators** - aimed at suppressing the body’s own immune reaction to the virus, in cases where the body’s reaction goes overboard and starts attacking the patient’s own organs.

⁸ Corresponds to number of safe to proceed Investigation New Drug applications (IND). Excludes INDs related to vaccines

- **Neutralizing antibody therapies** - may help individuals fight the virus and include manufactured antibodies, animal-sourced antibody therapies, and blood-derived products such as convalescent plasma and hyperimmune globulin, which contain antibodies taken from people who have previously had COVID-19.
- **Cell therapy** ([FDA, 2021](#)) - include cellular immunotherapies and other types of both autologous and allogeneic cells, such as stem cells, and related products.
- **Gene therapy** ([FDA, 2021](#)) - seek to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

Different drugs can be more or less effective at different phases of Covid-19. Generally, they can be thought of as being for early or moderate disease versus for moderate-to-advanced disease. The strategy early on is to block the replication of virus and prevent it from going from the upper airway into the lungs and other organ systems. However, experience over the past many months has shown that when one gets advanced disease, the hyper or aberrant inflammatory or immunological response contributes as much to morbidity and mortality as the actual virus replication itself ([Fauci, 2021](#)). Antivirals may work better at the beginning, and immune-response modulating drugs later, if the disease worsens ([Gallagher, 2021](#)). The diversity of therapeutic approaches being investigated is important because it rapidly expands understanding of the effect of different categories of potential treatments.

As of March 2021, more than 100 therapies were in late stages (phase III or IV) of human testing ([Biorender, 2021](#)), but approximately one year into the COVID-19 pandemic, just a handful of repurposed therapeutics have been approved to treat COVID-19 ([RAPS, 2021](#)):

- **Dexamethasone is recommended for use by WHO** ([WHO, 2021](#)) and has now been approved by multiple regulatory authorities including the European Medicines Authority ([EMA, 2020](#)), UK, India and Japan. It has also been included in many national COVID-19 guidelines. It is a steroid that decreases inflammation but does not directly inhibit viral replication; it has been clinically shown to reduce death among COVID-19 patients who are either on ventilators or receiving supplemental oxygen. Along with other corticosteroids, it is in widespread use, including in low- and middle-income countries, where dexamethasone is the main treatment for COVID-19. It is commonly available throughout the world, with existing manufacturing capacity globally.
- **Veklury (remdesivir)**, originally developed for Ebola and MERS/SARS coronaviruses, has received regulatory approval in Australia, Japan, India, and the UK, where it can be used for all hospitalized patients, as well as in the United States (although not in paediatric patients, who were included under a prior EUA). It is administered intravenously, usually over five days. Gilead, which makes remdesivir, posits that the drug cannot be made in pill form because the chemical construction would affect the liver. Instead, the company is working on an inhaled form of the medication that would be delivered through a nebuliser, which turns liquid medicines into mist ([Lovelace, 2020](#)). Support for remdesivir is not universal, as the WHO has recommended against it and some studies suggest there is insufficient evidence that it reduces death. Respondents noted that it is costly, hard to deliver, with benefits being limited (see Solidarity Trial findings under R&D section below).
- **Avigan (favilavir, favipiravir)** – originally used to treat influenza – might remove the virus from the airways. Despite the fact that its utility has yet to be shown in a large, randomised clinical trial, it has been approved to treat Covid-19 in China, Italy, Kenya, Russia, Saudi Arabia and Thailand.

However, results from a recent trial in Kuwait show that Avigan does not work in patients with moderate to severe Covid-19; trials will continue in North America on those with mild symptoms ([Financial Express, 2021](#)).

- **Tocilizumab**, an anti-inflammatory treatment given by injection, and **sarilumab** (both cytokine inhibitors) have also recently shown significant promise. The UK government-funded REMAP-CAP clinical trial showed that the risk of death is reduced by 24 per cent when given to patients within 24 hours of entering intensive care ([DHSC, 2021](#)). Most of the data comes from when the drugs were given in combination with a corticosteroid, such as dexamethasone, in addition to oxygen provision. They will be made available for use immediately in the UK.

There are also other drugs that have emergency use authorisation in different places. In the US, for example: convalescent plasma with definitive findings from the RECOVERY trial ([RECOVERY Collaborative Group, 2021](#)); Eli Lilly's monoclonal antibody bamlanivimab (in combination with etesevimab); Regeneron's antibody cocktail treatment REG-CoV2 (casirivimab and imdevimab); and the combination of the JAK inhibitor Olumiant (baracitinib) made by Eli Lilly and Gilead's Veklury (remdesivir). The South Korea Ministry of Food and Drug Safety has also conditionally authorized Regkirona (regdanvimab), a human monoclonal antibody from Celltrion.

Still in clinical testing are a number of other drugs that are in use to treat other ailments but have shown particular promise in treating COVID-19. These include: colchicine ([Swain & Buzby, 2021](#)), ivermectin ([TrialSite, 2021](#); [Hellwig & Maia, 2021](#)), budesonide ([PRINCIPLE Trial Collaborative Group, 2021](#); [Ramakrishnan et. al., 2021](#)), Aplidin (plitidepsin) ([Landauro et. al., 2021](#)), EXO-CD24 ([TOI, 2021](#)), Allocetra ([Enlivex, 2021](#)), and AT-527 ([Taylor, 2021](#)).

Oxygen therapy - It is critical to underscore the role of oxygen in any discussion of COVID-19 therapeutics. Timely oxygen therapy is currently recommended for COVID-19 patients with respiratory distress, hypoxemia, or shock ([WHO, 2020](#); [Long et al, 2021](#)). Despite being an essential therapy for COVID-19 (~1/5 COVID-19 patients will need oxygen), and WHO having listed medical oxygen as an “essential medicine”, wide gaps in access remain in most LMIC healthcare systems ([Every Breath Counts, 2020](#)). More analysis on oxygen is included under the Governance and Coordination Challenges below and in the Essential Supplies background paper.

Antibody treatments - Antibody treatments will be needed even after vaccines are in widespread use. They work in different ways: by targeting different parts of the coronavirus, and by providing protection. They hold the potential to prevent COVID infection if administered before the onset of symptoms, or before exposure to the virus, particularly in high-risk populations. They also seem to be effective as a therapy once people have already become sick. Accordingly, they can serve as a bridge to a vaccine and have a role to play after immunisation campaigns have been carried out. Initial analysis by the ACT-Accelerator (ACT-A) Therapeutics Pillar of more than 1,700 clinical trials identified COVID-19 monoclonal antibodies as one of the most promising treatment options for non-hospitalised patients – taken either as a preventative or at the early stage of the disease ([UNITAID, 2021](#)). Nonetheless, front runner monoclonal antibodies have to be infused and so imply a logistically challenging option in many settings especially for outpatient use. Moreover, recent findings demonstrate their efficacy is more limited with emerging variants. Other monoclonal antibodies, including cocktails, and new types of molecules, are in the pipeline showing better possibilities for use in low- and middle-income countries, including subcutaneous injections and possibilities for simplifying production.

Finding effective broad-spectrum antiviral drugs was described by respondents as being the holy grail for therapeutics. The lack of antivirals has been noted as a key current challenge, with the United States now calling for priority advancement of wide spectrum candidates that are easily administrable and have reached phase two clinical trials with proven safety profiles.

Unlike the vaccines landscape, where numerous procurement and delivery/administration trackers are publicly available, the same does not seem to exist for therapeutics despite gaps and transparency limitations ([UNICEF, 2021](#); [Knowledgeportal, 2021](#); [Duke, 2021](#); LSHTM, [2021](#); [Nikkei, 2021](#)). The majority of related information available through ACT-A is in reference to the therapeutics pillar, which highlighted key achievements to date, including:

- **Partners secured dexamethasone courses for up to 2.9 million patients in low- and middle-income countries through an advance purchase agreement, and have further secured initial mAbs production capacity for low- and middle-income countries in 2021 and 2022 (see What Worked under Manufacturing for more). The Wall Street Journal noted that orders of dexamethasone surpassed 2.8 million the week after the Recovery Trial released study results on June 16th, 2020, up from nearly 297,500 the prior week. This is based on data from Vizient Inc, one of the largest group-purchasing organizations in the US for hospitals, that showed demand across the facilities they manage increased by 183% the day the study was released and by 610% during that following week, with fill rates dropping from 97% to 54% ([Vizient, 2020](#))**
- **In collaboration with the BMGF (on behalf of the COVID-19 Therapeutics Accelerator), manufacturing capacity had been reserved for the development of Eli Lilly's potential COVID-19 monoclonal antibody for low- and middle-income countries. Investments would have reduced time to development and lowered manufacturing costs. However, with the emergence of variants, and the reduced efficacy of frontrunner mAbs, this was not pursued.**

2. Analysis of successes, challenges, and lessons learned

(1) Governance & Coordination

What Worked So Far

ACT-A Therapeutics Pillar: Background on the overall ACT-A can be found in the vaccine chapter. The Therapeutics Pillar of the ACT-A is co-convened by Unitaid and Wellcome, and aims to find the most promising treatments and ensure that low- and middle-income countries can access the benefits too. Workstreams include rapid evidence assessment (BMGF & Wellcome), market preparedness (Unitaid), and procurement and deployment (Global Fund & WHO). The key priorities in therapeutics for 2021 include: 1) ensuring the successful uptake of existing products, including medical oxygen and corticosteroids (e.g. dexamethasone), for up to 12 million severe and critical patients; 2) introducing new COVID-19 therapies for up to 100 million treatment courses across all use cases, subject to evidence supporting the use case and product availability; and 3) accelerating and intensifying research efforts to expand the therapeutics clinical pipeline, broadening the portfolio of effective tools, including combinations of therapeutics.

Separate from the therapeutics pillar of ACT-A, the **COVID-19 Therapeutics Accelerator (CTA)** was launched in March 2020 by Wellcome Trust, the BMGF and Mastercard, with additional funding from a range of donors. It takes an end-to-end approach in the drug development process and draws on expertise in drug and monoclonal development, chemistry, manufacturing and controls (CMC), supply chain, and regulatory affairs. Its governance model is meant to enable quick decision-making and allows it to provide fast and flexible funding to help remove bottlenecks in the drug development and scale-up process. The CTA is represented by donors in the Therapeutics Partnership of ACT-A. It is focused on providing support to identify drugs and treatments that can help prevent cases of COVID-19 among vulnerable populations and treat mild and moderate cases of the disease. With partners like Unitaid, the CTA is collaborating to support development of the procurement and delivery frameworks necessary for effective treatments to reach people in low- and middle-income countries. As of November 2020, the Accelerator had awarded over \$98 million in grants. ([Therapeutics Accelerator, 2021](#)).

Challenges

Weak Political Attention and poor funding: Overall, a broad range of factors have affected the R&D landscape and dynamics for therapeutics:

- **Fragmented research efforts and a great deal of work on re-purposing drugs that have not proven effective (few exceptions), while underinvesting in diagnostics;**
- **An overwhelming emphasis on (and funding for) vaccines, building on previous development of platforms (e.g., mRNA, adenovirus) and significant at-risk investment from US DARPA and NIH, versus uncertainty and smaller market incentives for therapeutics; and**
- **Lost time in therapeutics development and less clear signals to therapeutics manufacturers as a result.**

With an overwhelming portion of political and financing appetite going to vaccines, there has not been significant funding for COVID-19 therapeutics. This applies to all stages of the value-chain: however, R&D, manufacturing, and procurement are specifically highlighted. Expanding funding for manufacturing, as an example, will require a shift in mindset around IP and licensing, along with massive investments in technology transfer and manufacturing hubs in low- and middle-income countries. It will also be important to look at pots of money beyond overseas development assistance (ODA).

As set out in the latest ACT-A Prioritized Strategy and Budget ([March 12, 2021](#)), the Therapeutics Pillar needs \$3.2 billion to rapidly fund treatment research, prepare the market to produce treatments at scale, and deliver lifesaving treatments in low- and middle-income countries through end-2021 ([WHO, 2021](#)). Funds that are immediately made available will prioritize the successful uptake of existing effective products, including medical oxygen and corticosteroids (e.g., dexamethasone), the introduction of new COVID-19 therapies once benefit is established, and the acceleration and intensification of research efforts to expand the therapeutic clinical pipeline. This includes ensuring rapid deployment of therapeutics with upcoming clinical readouts if proven effective (e.g., small molecule novel antivirals and repurposed therapeutics).

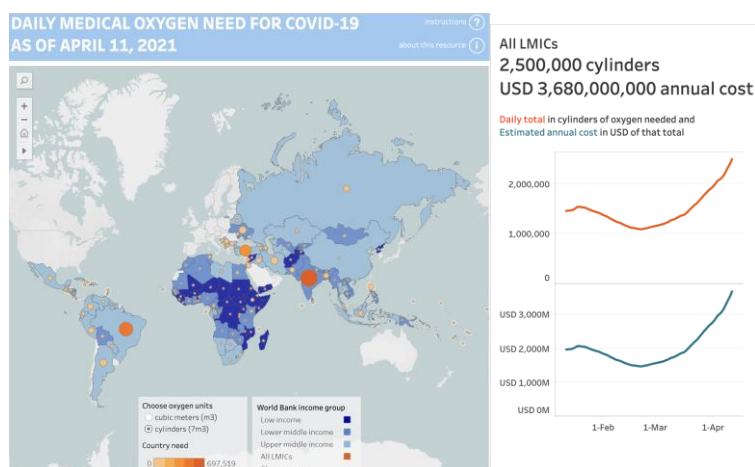
Gaps for therapeutics should be reduced slightly further after recent commitments from G7 leaders for 2021, including \$1.8 billion from Germany to be divided across all 3 pillars (and the health systems strengthening connector) of ACT-A, as well as \$79 million from Japan for COVAX AMC and UNITAID, and \$59 million from Canada for the ACT-A ([WHO, 2021](#)).

Insufficient attention to oxygen and clinical care outcomes: The ACT-A arguably initially focused too heavily on novel tools (i.e., biopharmaceutical products including mAbs and novel anti-virals) and not enough on enhancing clinical care outcomes and oxygen, which was initially situated under the health systems pillar. The discovery that dexamethasone could be repurposed as a valuable therapy for severe cases prompted a reassessment of where in ACT-A oxygen supply was situated, because it became clear that the limitation on effective use of dexamethasone was not the drug itself, since this is cheap and widely available, but rather the ability to provide oxygen support within the context of a broader clinical care package. Overall, oxygen had not received sufficient attention and support from ACT-A until this recent shift in priority and re-situating of oxygen under the Therapeutics Pillar.

More than half a million COVID-19 patients in low- and middle-income countries are estimated to need oxygen treatment every day. The lack of oxygen in countries has limited uptake of dexamethasone, one of the few therapeutics shown to be effective against COVID-19 thus far. Attempts to rectify these challenges started in February 2021 with the launch of the COVID-19 Oxygen Emergency Taskforce, which brings together key organisations working on oxygen access under the ACT-A Therapeutics pillar ([WHO, 2021](#)). New assessments show US\$90 million in immediate funding is required to meet the urgent need in up to 20 low- and middle-income countries. Unitaaid and Wellcome will make an immediate contribution of up to US\$20 million in total to catalyze the emergency response. Taskforce partners will work together to assess oxygen demand, work with financing partners, and secure oxygen supplies and technical support for a first wave of the worst-affected countries. A focus on country needs, working closely with them to identify issues, shortages, device availability, local production, etc. is now being made a priority. The success of the Taskforce will depend on robust assessments being generated at a country-level and prioritised appropriately by Ministries of Health.

In hindsight it could have been valuable to locate work on oxygen within the Therapeutics rather than Health Systems pillar from the start of the ACT-A response, and an institutional arrangement for oxygen should be part of a future system for vaccines, therapeutics, and diagnostics. In order to rapidly scale oxygen provision, the Global Fund's COVID-19 Response Mechanism (C19RM) will support provision of oxygen and related commodities, including through a fast-track funding mechanism ([Global Fund, 2021](#)). To communicate the urgency of investing in access to medical oxygen and related technologies to meet the needs of COVID-19 in Low- and middle-income countries, PATH also developed the COVID-19 Oxygen Needs Tracker. As of April 11, 2021 the need for oxygen amongst all low- and middle-income countries amounts to 2.5 million cylinders per day at an estimated annual cost of USD \$3.68 billion (Figure 13).

Figure 13: Daily Medical Oxygen Needs for COVID-19, April 11, 2021



Source: [COVID-19 Oxygen Needs Tracker](#)

Lack of therapeutics aggregator: The therapeutics landscape was more fragmented relative to the vaccine landscape, showing the lack of an experienced, central organization that can act as a global coordinator capable of resource mobilization (particularly for low- and middle-income countries) and end-to-end portfolio management. Multiple key interviewees noted the need for a dedicated CEPI/GAVI/COVAX-like entity, particularly for therapeutics. An expanded form of CEPI could potentially fill this role for therapeutics; however this would require capacity and is likely some years away, after the current vaccine-focused model is fully established.

Supply/product bias of the ACT-A model: While it has been a remarkable mechanism for promoting collaboration between entities, there may not have been enough focus on the end-to-end solution (e.g., how to run a testing and surveillance program; how to treat the sick; technical guidance and capacity building), which has become more of a challenge further downstream. Multiple interviewees noted there was likely too much focus on specific products (see note on lack of focus on oxygen and clinical care outcomes below under Lessons Learned).

WHO leadership challenges for pandemic therapeutics: It was noted that while WHO has dedicated expertise for vaccines, there is no dedicated center of energy for therapeutics, which was seen to be an obstacle for partners working in this area with WHO. For example, key informants noted that delays on the release of treatment guidelines for corticosteroids by WHO were a hinderance. There was confusion around the use of corticosteroids, given both beneficial and deleterious clinical outcomes having been reported in patients with other pulmonary infections, including evidence of delayed viral clearance in those with MERS and SARS ([Arabi et al., 2018](#); [Stockman et al, 2006](#)). Recommendations on the use of corticosteroids for COVID-19 are largely based on data from the RECOVERY trial, which showed that mortality at 28 days was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care, specifically in those who were mechanically ventilated or required supplemental oxygen at enrollment ([Recovery, 2020](#)). It was not until two months after the UK guidance changed based on these findings that the WHO guidelines also changed.

Lessons Learned

Governance/Institutional arrangements

- **Demand- and strategy-driven platform.** The pre-negotiated system for future outbreaks needs to have stronger technical leadership with clear views on treatment strategies to navigate R&D and

manufacturing. This function would need to be filled /supported by a strengthened WHO or other technical agency. The challenges encountered to advance R&D on therapeutics, particularly for early treatment with both novel and repurposed therapies, could have been prevented/alleviated with more concerted action at global level, and a more proactive R&D push for priority, fit-for-purpose therapeutics aligned with WHO-TPPs.

- Clear institutional leadership and funding, with CEPI and/or GAVI-type mechanisms, for therapeutics are critical. This will depend heavily on political will to make volumes available to low- and middle-income countries and whether the required funding is brought to bear – also a central lesson which likely matters more than the particular institutional structures.

Financing

- Integrated and strategic resource mobilization and allocation. The fragmented financing platform and fundraising efforts by the vaccines, therapeutics, and diagnostics pillars within the ACT-A led to competition between the three product areas and resulted in financing skewed to vaccines. More strategic and integrated resource mobilization through regular unearmarked funding from countries and optimal allocation through an integrated platform may improve the allocation issue of the limited funding. As suggested in the vaccines chapter, upfront predictable funding outside ODA would be needed to better prepare for future pandemics.
- The principle of staged-funding (e.g., secure funding for diagnostics first within an end-to-end fundraising framework) was also suggested to address the dearth of funding for therapeutics and diagnostics (and other essential supplies) relative to vaccines.

(2) Research and Development (R&D)

What Worked So Far

Screening of compound libraries: Compound screening is a method used to discover specific compounds with the potential of becoming promising candidates for pharmaceutical use. This potential is identified when compounds interact with the target protein during screening and could therefore be carried forward in the drug development process. This is a process whereby “hits” from screening are transformed into “leads” that can then be used for “lead optimization”. Engagement from companies was good with regard to allowing screening of their compound libraries. While in some ways this was due to commercial interest, there was also genuine interest in finding products that could work. Although there have not been any major therapeutic breakthroughs yet, machine learning-based models (i.e. artificial intelligence) trained on specific biomolecules have offered inexpensive and rapid implementation methods for the discovery and development of potential viral therapies ([Arshadi et. al., 2020](#); [Zhou et. al., 2020](#); [Omolo et. al., 2020](#)).

R&D of therapeutics for severe vs. early cases: R&D for management of severe cases worked well, in particular, relative to R&D for cases earlier in disease progression. It attracted more attention and generally progressed more smoothly. This was driven partially by rapid testing of re-purposed agents such as corticosteroids and tocilizumab in platform trials such as RECOVERY (listed below) rather than de novo R&D involving screening of compound libraries.

It became clear that solutions for severe cases were not generally applicable to earlier cases. R&D of therapeutics targeting earlier cases, in order to prevent disease progression, avoiding issues with oxygen and complexities of ICU management, should have been prioritized as well. Such was the focus of the ANTICOV trial (see below). A number of novel antivirals (NAVs) for early treatment - molnupiravir, now entering phase III trials, is the most advanced, along with antivirals from Pfizer and Roche/Attea - are currently showing promise.

Scientific Processes/Innovative Clinical Trials: While clinical trials investigating treatments and preventative measures for COVID-19 have been of highly varying quality, a few large international trials had rigorous and innovative designs (e.g. [adaptive](#) trials):

- **Solidarity Trial ([WHO, 2021](#)):** This international clinical trial, launched by WHO, is designed to find treatments for COVID-19 focusing on three outcomes: length of hospital stay, mortality and the need for assisted ventilation. It is being run in more than 30 countries and has enrolled almost 12,000 patients in 500 hospitals, representing varied and evolving standards of care, burden of disease, capacity to administer treatment, and treatment options. It is one of the largest international randomised trials. After several months of study, the steering committee released interim results in mid-October 2020. The data show no evidence of a meaningful benefit on in-hospital mortality for hydroxychloroquine, lopinavir, or interferon beta-1a when averaged across a wide range of settings, either overall or in important subgroups. Viewed collectively with previous studies, it sends the clear message that these drugs as currently used should no longer be considered viable treatment options for Covid-19 ([Harrington et al, 2021](#)). The case for the continued use of remdesivir is more nuanced. While no substantial mortality benefit was noted with remdesivir across a variety of health care settings, other data suggest that the drug may still have an important role ([Biegel et al, 2020](#); [Spinner et al, 2020](#); [Wang et al, 2020](#)). Its benefit may be its ability to change the course of hospitalization in some patients, but not to expect substantially reduced mortality. Launching and executing this ongoing trial has been described as a “remarkable achievement” with randomization at hospitals across a range of HIC and LMIC countries, rapid and widespread enrollment, collection, recording, and transmission of a small amount of high-information data ([Harrington et al, 2021](#)). The trial averages over a source of heterogeneity not normally encountered with more conventional designs.

Recovery Trial: This innovative UK platform for trialling COVID-19 drugs is responsible for delivering clear evidence about the effectiveness of dexamethasone and tocilizumab, amongst others. Other important contributions include provision of sufficient evidence to rule out several candidates. This is another large enrolment study of possible treatments for people admitted to hospital with severe COVID-19 infection. Described as one of the positive outcomes within the therapeutics space, the set-up and approach of the Recovery Trial is cited as a model that effectively streamlined the clinical trial process:

It had a short, flexible protocol – just 20 pages long – that laid out the design and data and regulatory requirements, and allowed trial arms to be halted or added. It received ethical and regulatory approval in just 9 days, compared with the standard 30–60 days. Its recruitment procedures were straightforward, with only a two-page consent form and a one-page bedside form to be completed by clinicians. Patients who tested positive with COVID-19 who entered any of the United Kingdom’s 132 National Health Service hospitals were invited to participate. Over 5,000 patients were enrolled in the first month after it launched. It accelerated data collection and processing through [NHS DigiTrials](#).

It quickly made results public — the announcement was followed by a [pre-print on the medRxiv server](#) and journal publication within a month.” ([Mather, 2020](#))

It leveraged an adaptive clinical trial design. A traditional phase III trial “must recruit patients to its own control group and test just one hypothesis... whereas an adaptive trial platform allows researchers to [simultaneously test multiple interventions](#) against a single, shared control arm, add and eliminate treatments as the trial progresses, and update the study design as the treatment landscape changes.” ([Plump, 2020](#))

Advances and investments in monoclonal antibodies were seen to be a positive given the increasing importance of therapeutic mAbs ([Lu et. al., 2020](#)). Current antibody drugs have increasingly fewer adverse effects due to their high specificity and have accordingly become the predominant class of new drugs developed in recent years. Over the past five years, antibodies have become the best-selling drugs in the pharmaceutical market, with eight of the top ten bestselling drugs worldwide being biologics in 2018. While the market for therapeutic antibody drugs has experienced explosive growth as new drugs have been approved for treating various human diseases, including many cancers, autoimmune, metabolic and infectious diseases, their utility is only expected to grow globally. As noted earlier, analysis by the Therapeutics Pillar of ACT-A identified COVID-19 mAbs as one of the most promising treatment options for non-hospitalised COVID-19 patients. However, in January 2021 the partnership noted the growing challenges deploying mAbs as a monotherapy due to the rise of variants. In addition, access challenges including supply restrictions, to a lack of formulations adapted for outpatient care, are a considerable barrier for many mAbs. This resulted in a more nuanced approach to mAbs going forward focused on combination therapies that may be resistant to variants and formulations that were easier and cheaper to deliver.

Challenges

A lack of “hits”: Despite early energy around several promising novel and repurposed therapeutics, most screenings and existing product trials have been unsuccessful, with the exception of a handful of products noted above in the Landscape section. A more formal global mechanism for supplying compound leads, taking them through animal models, preclinical, phase I, and then feeding them onward into larger trials is necessary.

Variants: The emergence of variants has added to the difficulty of developing new tools such as monoclonal antibodies ([King, 2021](#)). The variants we have seen so far include alterations to the spike protein and the binding site for many mAbs. Thus, going forward mAbs may be needed in combination or targeting regions that are less commonly changed in variants. Vaccines will not reach the coverage levels required to reduce transmission nor further mutations for some time, and so there is a huge incentive to scale-up testing and reduce prevalence, of which mutation is a function.

Poor quality trials, data, and data sharing: Although there are a few key large high-quality RCTs, the overall quality of trials and data was poor. Of the thousands of clinical trials investigating treatments and preventative measures for COVID-19 ([COVID-19 Clinical Trial Tracker, 2021](#)), only 7% of all trials were deemed to be well designed and powered, with many not designed for or resulting in actionable findings. In addition, whether data quality was good or bad, a good mechanism for data-sharing was seen to be a gap.

The Standards-Based Active Guidelines Environment (SAGE) model, focused on developing a universal framework for encoding and disseminating electronic clinical practice guidelines ([Tu et. al., 2007](#)), has

worked relatively well for gathering genomic sequencing data, and this model should be studied further. While challenges have been less acute in the therapeutics space thus far, due to most recommended medicine being host-directed, this is expected to change as more tools targeting earlier phases of the disease and against the virus itself (e.g., mAbs and VAVs) are deployed. There are now approximately 650K genome sequences available. Even so, approximately half are from just 4 or 5 countries, with most coming from the UK. There are still major gaps from the African and Middle East regions. Many researchers are reluctant to share sequences into the system fearing that someone else will publish a related paper and get credit. Systems are needed that build trust, with the right terms and conditions to reassure researchers.

Appropriateness of WHO's role: Despite successes in the Solidarity trial, interviewees also described the management of clinical research programs by WHO as being out of their purview, area of expertise and core functions. It also creates conflict of interest for the WHO to engage in making norms, guidance and approvals, while at the same time conducting clinical trials. It was suggested that the focus of WHO, rather, should remain on developing guidelines, setting standards (e.g. trial design), pre-qualification (PQ), allocation frameworks, and the like.

Not enough focus on regional trial sites: Interviewees noted that there needs to be more focus on regional trial sites. This means more expense and capacity to do them right. African leaders and scientists, for example, called for more clinical trials for therapeutics and vaccines to take place in Africa early on. While there are hundreds of trials for possible COVID-19 drugs taking place globally, there are very few in Africa. One of the few good examples is the ANTICOV Trial, a collaborative effort launched by an international network of research institutions and 13 African countries, and supported by ACT-A through Unitaid co-funding with the German government ([UNITAID, 2020](#)). It aims to find cheap, readily available drugs that can keep those suffering from COVID-19 out of hospital, so that already-weak health systems are not overwhelmed. More specifically, the trial seeks to find a drug that reduces by half the likelihood that mild COVID-19 cases progress to severe illness. ANTICOV leveraged the African Vaccine Regulatory Forum (AVAREF), a platform established by WHO that brings together National Regulatory Authorities (NRAs) and national Ethics Committees (ECs) on the African continent with the objective of strengthening clinical trial regulation in Africa ([WHO, 2020](#); [DNDI, 2020](#)). More strategic and coordinated investment in clinical trial capacities across the world will be a critical part of preparedness in the case of future pandemics.

Regulatory over-caution: Key informants noted that there were challenges with getting trials started in some low- and middle-income countries with some regulators being much more, perhaps overly, cautious. For example, Indonesian regulators wanted Aspirin (part of the Recovery study protocol) to have experimental drug labelling, despite being a long-proven drug. Addressing such bottlenecks could help create greater efficiencies.

Lessons Learned

Regulation, guidance, and procedures to expedite and ensure high-quality clinical testing: Drug development is a multistage process, typically requiring more than five years to assure safety and efficacy of a new compound ([FDA, 2021](#)). Several national regulatory agencies, such as the EMA, FDA, and Health Canada approved procedures to expedite clinical testing ([FDA, 2020](#); [EMA, 2021](#); [Oakes, 2020](#)) and approval, which were deemed to be crucial during an emergency situation. In India too, regulators relaxed norms ([Bhave, 2020](#)) to great benefit, demonstrating the importance of having

simplified and faster processes during health emergencies. Such emergency protocols, that can come into play quickly, must be a standard guiding all country regulators.

At the global level, the WHO's R&D Blueprint for COVID-19 ([WHO, 2020](#)) and the coordinated global Research Roadmap ([WHO, 2020](#)), both of which build on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, were seen as being instrumental in guiding R&D processes and priorities. In this way, the role of the WHO in setting norms and standards (e.g., for animal models and lab assays), research priorities, definitions, etc., as early as possible, to bring clarity, was indispensable. An example of a useful procedure included having infrastructure linking numerous hospitals (i.e., networks), which was seen to make a big difference with regard to clinical trial conduct and recruitment. Similarly, experience gained in the development of vaccines for Ebola provided important lessons in the regulatory, clinical, and manufacturing process for application to SARS-CoV-2 ([Wolf et. al., 2020](#)).

A need for global coordination of high-quality clinical trials: Rather than having many trials of poor quality, it would make sense to have a smaller circle of people/organizations doing RCTs well. These could be standardized, globally distributed across a well-trained network of regional trial sites, centrally coordinated, and allow for head-to-head comparisons (e.g. Solidarity). For example, many trials were underway for hydroxychloroquine, with a lot of capacity being wasted on well-intentioned but poorly set-up trials that led to counterproductive media attention and poor-quality information. Many felt that WHO was not ideally positioned to play such a role.

Widely employ R&D best practices and tools

- **Development and effective use of Target Product Profiles (TPPs).** Adherence to TPPs ensure that important questions are asked early on, for example: why are we doing this research? What is the objective for this product candidate? What are critical country perspectives relating to route of administration (e.g., practicality of intravenous delivery), delivery setting, technical proficiency and dosage requirements, etc.? For example, while TPP was eventually developed for outpatients (i.e., mild to moderate cases), it arrived later, such that many studies rolled out not looking at the same criteria. This had knock-on effects with development of WHO guidelines—either for or against certain treatment—being made based on strong data from Solidarity and Recovery, but not specific to outpatients. Thus there was a disconnect with regard to guidelines for earlier cases. This has important implications for how trial designs (e.g., study power) link to guideline development (e.g., looking at mortality vs. progression to severity).
- **Early R&D phases and leveraging artificial intelligence (AI):** In the big data era, artificial intelligence (AI) and network medicine offer the complex application of information science to defining disease, therapeutics and identifying targets with precision. There is a need for consultation on preclinical and clinical models for research, particularly in vitro and animal models, as well as further investigation of the role of AI in compound identification.
- **Off-label use of therapeutics under EUAs should be discouraged.** It can harm patients, it interferes with clinical trials, and it can disrupt the entire R&D program for the disease being studied, as certain drugs may become standards of care (e.g. Tamivir) resulting in unproven comparators.
- **Observational data should not be used to advance therapeutics.** These study designs are meant to be hypothesis generating. Rather, RCTs work well, are rigorous in their design and provide more definitive answers. They can be set up quickly and recruit participants at-scale. Of course, there

are caveats, as they need to be well managed and designed. Many trials have been a huge waste of time, with many that have been only partially informative and too small to provide sufficient power to the study, and focussing on biomarkers as opposed to clinical endpoints.

(3) Manufacturing at Scale

Challenges

As with vaccines, manufacturing capacity is identified as a challenge area for therapeutics. While there are several potential bottlenecks in the end-to-end manufacturing and supply chain, various analyses have identified additional key steps that could stand in the way of large-scale COVID-19 therapeutics production, requiring cross-industry solutions ([Dilenge et al, 2020](#)). These include:

- **Biologic drug substance production**
- **Sterile fill and finish capacity**
- **Lyophilization capacity**
- **Industry regulation including** ¹⁾ Importance of rapid response from industry regulators on development questions; ²⁾ need to accelerate manufacturing technology transfer and facility registration processes to expand available capacity; and ³⁾ need for international regulatory harmonization; and
- **Trade policy and competition regulation including** ¹⁾ prevention of potential export restrictions; ²⁾ unintended consequences of compulsory licensing; ³⁾ Financial risk and inefficiencies of locking up speculative capacity

Lessons Learned

- **Diversification and increase in manufacturing capacity:** There has been too much focus and dependency on manufacturing concentrated in a few countries that can manufacture at scale. A need for a network of regional ‘ever-warm’ biologics (e.g., mAbs) and small-molecule therapeutic facilities in configurations to mitigate geopolitical risks was identified. Just like vaccines, there are no well-funded international agencies with clear mandate to support the strengthening of manufacturing capacity.
- **Use of contract manufacturers at the outset can greatly increase availability of countermeasures.** In addition, being able to reserve capacity for LMIC drugs is an effective approach.

(4) Procurement

What Worked So Far

Partners secured dexamethasone courses for up to 2.9 million patients in low- and middle-income countries through an advance purchase agreement. By mid-April 2021, UNICEF has delivered over 1.1 million units of Dexamethasone products, oral and injectable formulations, in 15 low- and middle-income countries.

Challenges

Funding: As noted under governance, funding has been a challenge for the therapeutics pillar.

The Global Fund Board has approved the extension of the COVID-19 Response Mechanism (C19RM), a mandate beyond their original remit. They will continue to provide additional support to partner countries. How much of each country’s C19RM Base Allocation should be devoted to securing urgent COVID-19 health products through the fast-track process will depend on individual country

circumstances. Countries are being strongly encouraged to consider individual country contexts and reflect programmatic needs to submit considerably more than the anticipated half of base C19RM Base Allocation at portfolio level to ensure available funding of US\$900 million is maximized and fully deployed in an efficient manner.

Infodemic in procurement: The infodemic was not just a challenge for members of the public, but for governments trying to procure what they needed for effective pandemic response ([WHO, 2020](#), [UNDP, 2020](#)). Governments had to collate huge quantities of information from different sources, with no tools to differentiate between reliable and unreliable information and knowledge, even for high-level decision-making processes.

Lessons Learned

Stronger end-to-end coordination: Need clearer linkage of development efforts to clear ownership of procurement for therapeutics.

Timely knowledge and information hub for countries: A reliable and agile knowledge and information hub with clear and timely guidelines is needed, not only for research, but also for procurement and best practices (e.g., How other countries are dealing with common problems like access to reagents or machines; transparent prices that countries should be paying; sources for products; etc.). This could be established either at regional and/or global levels.

Better access to supranational architectures for pooled procurement: While there are examples of effective regional procurement initiatives (e.g., AMSP), such mechanisms were not universally available. Key informants noted that some Latin American countries, for example, did not have the means to collectively procure supplies with other countries and benefit from economies of scale. Mechanisms put in place both prior to the pandemic and during did not work effectively in many instances with some countries noting they did not find a way to improve access to quality diagnostics or oxygen, for example.

Existing mechanisms should be leveraged, where possible. Countries have different mechanisms (e.g., revolving funds, strategic funds, contraceptive funds) already in place that they contribute funds to, are used to working with, and have legislative approvals for. In some cases countries have already made changes to their regulatory frameworks in order to put funds towards these mechanisms. There is a need to learn from these funds and adapt them for use in emergencies. This may present a good opportunity to align mechanisms already put in place under the UN.

De-linkage of R&D costs from product pricing. Given significant public investment in R&D, there are reasonable expectations that affordability should not be a concern, and that there must be a requirement for a public return on those investments, including collaboration (e.g., tech transfer, patent pooling, IP sharing, etc.) over competition, affordability and equitable access. Astra Zeneca vaccine pricing through COVAX reflected such an approach, however, such de-linkage approaches remain ad-hoc, fragmented and limited (Bulc & Ramchandani, 2021).

(5) Allocation

What Worked So Far

A fair and equitable allocation mechanism for potential new therapeutics is being developed to ensure that those most in need benefit from such products, particularly in cases where supply might be constrained (e.g., novel antivirals, novel antibodies).

No allocation mechanism is currently required for dexamethasone due to its sufficient supply – it is a repurposed small molecule with manufacturing capacity already at scale and a well-established global supply chain. It is also reserved for severe and critically ill patients, and therefore current supply is expected to meet demand.

Challenges

Equitable Access: In therapeutics we have seen a free-for-all in terms of timing and the proportion of allocation to current products. This is due to the limited number of successful products proving effective against COVID-19, as well as legal limitations on the quantity of drugs that countries with the ability to pay are able to procure.

In June 2020, for example, Gilead agreed to provide the US with 500,000 doses of remdesivir, which at that time was perceived to show promise in reducing the recovery time for patients with COVID-19. This quantity represented Gilead's full production capacity at the time for July and 90% of its capacity for August and September. These attempts to secure preferential access to medicines, so-called treatment nationalism, jeopardize supplies of life-saving treatments and vaccines available elsewhere, and jeopardize global equitable distribution of such products more generally. Such developments reflect political dynamics, but also demonstrate the power patent holders have in controlling access to life-saving healthcare, determining who obtains access first and at what price ([McMahon, 2021](#)). Current mechanisms like the Medicines Patent Pool ([Worley, 2020](#)) and the COVID-19 Technology Access Pool (C-TAP) ([Worley, 2020](#)) can help, but approaches need to be adapted for COVID-19 in a pragmatic way.

Lessons Learned

Clear guidance on use cases is needed: Use cases help drive demand. Demand and global allocation go hand-in-hand. Fair allocation does not happen automatically, and coordination is needed.

(6) Delivery

Challenges so far

Low number of WHO-recommended COVID-19 therapeutic products, especially for outpatient care: Overall, there is still limited experience on COVID-19 therapeutics delivery due to the lack of treatments that have been authorized for use in COVID-19, failure to show efficacy/safety of several of the candidate drugs being evaluated, and delays in the generation of clinical evidence from promising candidates still in the pipeline. For patients with mild COVID-19, only symptomatic treatment such as antipyretics for fever and pain, in addition to supportive measures, are recommended.

Lower stakeholder attention on therapeutics versus vaccination: One of the key issues observed is the limited focus on therapeutics by key stakeholders due to the primary focus on scaling up vaccination programs. Nevertheless, challenges along the continuum of care continue to exist, e.g., due to persisting shortages in medical oxygen and uncertainty about other therapeutics' access at the point of care. Some of those issues are chronic (especially in fragile health systems), but acute spikes in demand due to COVID-19 create additional urgency.

Challenges linked with in-hospital management of severe cases: For patients having progressed to severe disease, a high number of challenges have been encountered to ensure continuous access to oxygen in low- and middle-income countries as well as a number of ancillary and supporting elements. Commodity-related challenges are additional to challenges encountered in adapting already fragile capacity of inpatient care in many low- and middle-income countries. To tackle these issues, there is a strong need for additional in-country technical assistance on therapeutics, ensuring better visibility on countries' situations regarding therapeutics availability and to quickly implement therapeutics solutions at scale. C19RM will be instrumental on providing support to address these challenges.

Translating demand into delivery: Having supply in the first place may be a challenge for certain therapeutic products once their need is established (e.g., oxygen, mAbs, NAVs, etc.). In parallel, the Therapeutics Pillar along with UNICEF and the Global Fund assessed capacity to supply and define best practices, mechanics, and the most pragmatic approaches to supply when relevant. A real problem noted relates to how best to support translating need into demand from countries (e.g., dexamethasone and oxygen), a challenge that will be more pronounced for earlier therapies.

Lessons Learned

Need for concerted action to push packages of care: Overall, the focus should be on concerted actions to deliver the most impactful packages of care at different steps along the continuum of care, ranging from test-and-treat strategies for mild/moderate use cases to clinical care for severe/critical cases. As part of that, it will be critical to manifest the importance of oxygen being seen as a lasting end-to-end priority. A coordinated push for COVID-19 packages of care (from early treatment to management of severe cases) will be a key priority for the upcoming months, and the availability of the Global Fund C19RM funds offer the opportunity for a step change on therapeutics delivery.

CHAPTER 4 – IN-DEPTH REPORT ON DIAGNOSTICS

1. Overview of the current state

Accurate and rapid diagnostic tests are critical to achieving control of COVID-19. Testing continues to play an essential role in the pandemic, enabling patient care, facilitating surveillance (including sequencing) to inform policy and product development, as well as providing decision makers with vital data to inform test-trace-isolate strategies and other public health measures including lockdowns. The goal of a testing strategy is to identify infected individuals with the aim of reducing onward transmission. Any strategy should include a choice of a test or tests, and how to use them. Key principles for testing include: (i) the importance of fast turnaround times; (ii) the relationship between test positivity and infectivity; and (iii) the ease of use from sample collection to execution of the test ([Boehme, et. al. 2021](#)). These are applicable to all SARS-CoV-2 testing policies for public health use, along with cost considerations relating to high-volume testing.

Currently available diagnostic tests for COVID-19 fall into three main categories:

- **Molecular tests – used to detect viral RNA in patient samples from the upper and lower respiratory tract (e.g., using nasal or oropharyngeal swabs, sputum, or bronchial lavage). These tests are highly sensitive and specific but can only be used optimally from 1–7 days post-onset of symptoms. Molecular testing is also a prerequisite for genetic sequencing.**
- **Antigen detection tests – used to detect viral proteins in samples from both the upper and lower respiratory tract and can be used in asymptomatic individuals shedding virus, and from 1 to 14 days after onset of symptoms. They may not be as sensitive as molecular tests, but can serve as a rapid means of triaging suspected cases in settings where access to molecular testing is limited.**
- **Antibody tests – used to detect antibodies produced in the blood of infected patients starting from 5 to 10 days after infection. A positive IgM (type of antibody) antibody test in patients who fulfil the clinical case definition for COVID-19 is strongly suggestive of recent infection. IgG antibodies can persist for a long period and usually provide evidence of past infection.**

FIND (the Foundation for Innovative New Diagnostics) co-leads the diagnostics pillar of the ACT-A. They are collating an overview of SARS-CoV-2 tests that are commercially available or in development for the diagnosis of COVID-19. Their tracker lists over 1000 tests that have been commercialized ([FIND, 2021](#)). Approximately 41% are antibody assays, 38% molecular assays, and 19% antigen assays. Of these, FIND has identified 177 commercially available antigen rapid diagnostic tests (Ag-RDTs) (89%) and point of care molecular (i.e. RNA) tests (11%), each taking less than 90 minutes (many under 30 minutes) to generate a result ([FIND, 2021](#)). Nonetheless, by April 2021, only three companies with RDTs have been granted WHO Emergency Use Listings (EUL) for the category of Ag-RDT – Abbot, SD Biosensor ([FIND, 2020](#)), and Premier Medical Corporation ([WHO, 2021](#)). WHO along with key stakeholders has defined minimum performance specifications for point of care Ag-RDTs in a Target Product Profile ([WHO, 2020](#)). A number of other Ag RDTs are at various stages of development and assessment, with progress of active applications in the emergency use listing assessment pipeline being published intermittently (WHO, 2021). Overall, 26 diagnostic tests have been granted WHO EUL, also including 23 molecular tests and 1 antibody test, a pre-requisite for provision through ACT-A (WHO, 2021; WHO, 2020).

While all types of tests are considered important in developing a successful COVID-19 response strategy, the reverse transcriptase polymerase chain reaction (RT-PCR) molecular test is widely used as the reference standard for diagnosis of COVID-19. However, RT-PCR tests also have limitations, including potential false-negative results, changes in diagnostic accuracy over the course of the disease, and

precarious availability of test materials. Global competition for reagents and supplies, for example, has been a major challenge with regard to molecular tests, having severely slowed down testing capacity, particularly in resource-constrained settings ([Peeling et al, 2021](#)). In addition to being resource intensive, this form of nucleic acid amplification testing (NAAT) is also not widely accessible in many low- and middle-income countries, as it requires specialized lab technicians and equipment. This limits the ability to conduct the volume of tests needed and rapidly deliver results to those tested. While shipping clinical samples to centralized laboratory facilities has been organized in many countries, it is also associated with significant delays in results reporting of results, often negating impact on clinical decision-making and transmission interruption ([WHO, 2020](#)). Normally, results are available in less than two hours, but many countries are seeing delays of up to seven days ([McGarry, 2020](#)).

An alternative assay that can alleviate some of the bottlenecks created by molecular testing would be antigen testing. Ag-RDTs are the primary diagnostic test for detection of active SARS-CoV-2 infection in decentralized settings where timely molecular testing is not available. These simple-to-use tests offer the possibility of rapid case detection, especially of the most infectious patients in the first week of illness, at or near the point of care. Antigen tests diagnose active infection by detecting SARS-CoV-2 viral proteins in different specimen types. They are available as single use, lateral flow Ag-RDTs that can be visually read or processed or read using a small portable device. Both can be done outside the laboratory and some provide a result, some within 15–20 minutes. These rapid tests can be produced faster and more cheaply, in larger quantities, for large scale deployment. Although these tests can be highly specific, in comparison with RT-PCR, they lack sensitivity. Owing to this increased risk of false-negative results, they are generally considered adjunct to RT-PCR tests ([Mertens et. Al., 2020](#); [Maket. al., 2020](#)). For this reason, WHO initially advised against RDT testing in low-prevalence settings without NAAT confirmation until there were significantly more data from high-quality studies confirming very high specificity (>99%) of one or more commercialized Ag-RDT test kits ([WHO, 2021](#)). These data have now started to come online (Figure 14):

Figure 14: Examples of COVID-19 antigen-detection RDTs

	Sample type	Time of sample collection*	Result reading	Sensitivity, specificity†	Comments
Abbott BinaxNOW, USA	Nasal swab	0–7 days	Visual, 15 min	97%, 99%	WHO Emergency Use Listing; US FDA Emergency Use Authorization; app for results; influenza A and B tests available
Abbott Panbio, USA	Nasal swab, nasopharyngeal swab	0–7 days	Visual, 15–20 min	93%, 99%	WHO Emergency Use Listing; US FDA Emergency Use Authorization pending
Access Bio CareStart, USA	Nasal swab, nasopharyngeal swab	0–5 days	Visual, 15–20 min	88%, 100%	US FDA Emergency Use Authorization
BD Veritor, USA	Nasal swab	0–5 days	Instrument, 30 min	84%, 100%	US FDA Emergency Use Authorization
LumiraDx, UK	Nasal swab	0–12 days	Instrument, 12 min	98%, 97%	US FDA Emergency Use Authorization
Quidel Sofia SARS Antigen Fluorescent Immunoassay, USA	Nasal swab, nasopharyngeal swab	0–5 days	Instrument, 20 min	97%, 100%	US FDA Emergency Use Authorization; does not differentiate between SARS-CoV and SARS-CoV-2
Quidel Sofia Flu and SARS Antigen Fluorescent Immunoassay, USA	Nasal swab, nasopharyngeal swab	0–5 days	Instrument, 20 min	95%, 100%	US FDA Emergency Use Authorization
SD Biosensor, South Korea	Nasal swab, nasopharyngeal swab	Not stated	Visual, 15–30 min	97%, 100%	WHO Emergency Use Listing
Premier Medical Corporation Private Limited, Sure Status COVID-19 Antigen Card Test	Nasopharyngeal swab	Not stated	Visual, 15–20 min	94%, 100%	WHO Emergency Use Listing

Data from FIND. SARS-CoV=severe acute respiratory syndrome coronavirus. FDA=Food and Drug Administration.

*Days after symptom onset

† Data from manufacturers

The WHO opened an Expression Of Interest (EOI) process to allow developers to submit Ag-RDTs for Emergency Use Listing (EUL) in late February 2020, with provisional performance targets released later in the year in the TPP. While the first generation of reader-free Ag RDTs did not meet the performance standards needed for response, scouting activities by FIND and other diagnostics pillar partners identified several products in the pipeline whose performance met the TPP performance levels and could be manufactured at scale. After monitoring the evolution of the market, including active engagement with developers globally and quantification of the expected supply in the market, it became clear that at least until early 2021 there would likely be very few developers on the market with a reader-free Ag-RDT with WHO EUL approval that could be manufactured at scale. This reality was borne out, and there remains a need for more Ag-RDTs to achieve WHO EUL that meet technical specifications and can be manufactured at scale. Alternatively, ACT-A could consider leveraging the approvals of well-established regulatory authorities other than WHO (e.g., FDA Emergency Use Authorization). Developers of the first two approved Ag-RDTs reported that demand from HICs could have absorbed supply “several

times over” leaving limited volumes for low- and middle-income countries without volume guarantees from ACT-A.

The ACT-Accelerator is aiming to supply a total of 900 million COVID-19 diagnostic tests to low- and middle-income countries during 2021 (WHO, 2021), 75% of which must be deployed in decentralized settings (i.e. primary healthcare, community-level care, hospital triage) ([WHO, 2020](#)). This is in addition to tests provided through domestic planning and procurement. Key achievements to date include ([FIND, 2021](#)):

- 3 Ag RDTs approved by WHO for emergency use ([FIND, 2020](#))
 - A full access package includes WHO policy guidance on the use of Ag-RDTs, manufacturer volume guarantees for low- and middle-income countries, catalytic funding to assist governments to deploy the tests and an initial US\$50 million procurement fund from GFATM.
 - Several rapid, point-of-care antigen tests that are being assessed by WHO for EUL ([WHO, 2021](#)).
 - Expedited market introduction of these tests in multiple low- and middle-income countries is being supported through the Africa CDC, Unitaids, FIND, CHAI, and their partners.
 - 120 million tests (of the targeted 900 million for 2021) reserved for LMIC purchase, with the Bill and Melinda Gates Foundation (BMGF) executing volume guarantee agreements with Abbott and SD Biosensor, and tests priced at a maximum of US\$5 for low- and middle-income countries ([WHO, 2020](#)).
 - A set of new agreements, the first of which is with Premier Medical Corporation (PMC) of India, followed an open call for Expressions of Interest (EOI), launched last year by FIND and Unitaids on behalf of ACT-A, to drive equitable access to fit-for-purpose Ag RDTs for COVID-19 ([FIND, 2021](#)). Technology transfer, scale up and automation of manufacturing capacity will enable over 250 million high-quality tests to be made available for low- and middle-income countries at a price of less than US\$2.50 per test, cutting in half the cost of rapid COVID-19 tests for Low- and middle-income countries.
- [Performance evaluations ongoing](#), including assessment of digital tools for screening and diagnosis, with data published on a rolling basis.
- Procured over 34 million molecular tests and 31 million Ag-RDTs (of the 120 million reserved) for low- and middle-income countries; more information on procurement available from [the Global Fund and Diagnostics Supply Consortium](#).
- Deployed catalytic funding for set-up and accelerated in-country deployment support activities, policy mapping, operational research, and catalytic funding, including in over 15 countries for Ag RDT roll-out.
- Finalized data governance framework to guide ownership and management of diagnostic data, as well as implementation guide and modular training package for RDTs.

2. Analysis of successes, challenges, and lessons learned

(1) Governance & Coordination

What Worked So Far

ACT-A Diagnostics Pillar: The ACT-A Diagnostics Pillar is co-convened by FIND and the Global Fund. Workstreams include R&D of tests and digital tools (working group leads: BMGF and Praesens, respectively), market readiness (Unitaid & FIND), supply (WHO & Global Fund), country preparedness (Africa CDC and PAHO), data foundation and modelling (World Bank and Imperial College London),

strategic private sector engagement (WEF, BMGF, Mayo Clinic Labs, & Water St), and advocacy/community engagement (WACI Health, Global Fund Advocates Network, and STOPAIDS). Updated priorities over the coming year have been defined as: (i) Rapidly identify game-changing diagnostics and securing equitable access to tests; (ii) Stimulating rapid and effective uptake in countries; (iii) driving development and at-scale availability of affordable, transformative, digitally-integrated tests ([WHO, 2021](#)). Beyond March 2021, the focus will also be on making a mass-produced, US \$0.50 test available to everyone, everywhere, aiming to procure a total of 900 million high quality tests procured by the end of 2021.

Despite a lack of funding, the diagnostics pillar has made good progress. The world had manual RT-PCR tests within a few weeks of the SAR-CoV-2 pathogen being identified, automated (high volume) RT-PCR tests by late April 2020, and the first Ag-RDT tests meeting WHO performance criteria by September 2020. Moreover, the Diagnostics Pillar ensured that the automated RT-PCR and WHO-approved Ag-RDTs were made available in low- and middle-income countries in the same month in which they became available in HICs (albeit at low volume). It was arguably the first pillar to provide countries with products, the first to run a multi-partner equitable allocation model, the first to construct a package deal comprising volume guarantees, scale purchasing, normative guidance, and technical assistance, and the first to deliver on arrangements to secure significant reductions in pricing. It was also the first to include substantive, representative inclusion of civil society organizations (CSOs).

Expanded Global Fund function helping address poor funding. The Global Fund has played a role beyond its original mandate to help fill the COVID-19 diagnostics gap, deploying US \$1 billion through its COVID-19 Response Mechanism (C19RM) in 2020, and has recently secured significant new funding (> US \$3.7bn) to help meet needs. A significant portion of the > US \$3.7bn of funding to flow through this mechanism will be dedicated to diagnostics, including procuring tests, strengthening laboratories, running surveillance and test and trace interventions.

Challenges

Poor funding: Lack of funding was identified as the biggest challenge for the Diagnostics Pillar, which requires total funding of \$8.9 billion in 2021, according to the most recent update ([WHO, 2021](#)). While there were attempts to create a collaborative purchasing mechanism, particularly for automated RT-PCR, the money was just not there. When quality Ag-RDTs became available, the pillar managed to secure volume guarantees, but they were unable to use them due to a lack of funds. There has been what was referred to as “a structural underinvestment and undervaluing of diagnostics.”

Gaps for diagnostics should be reduced slightly further after recent commitments from G7 leaders for 2021, including \$1.8 billion from Germany to be divided out across all 3 pillars (and the Health Systems Connector) of the ACT-A, as well as \$79 million from Japan, and \$59 million from Canada for the ACT-A ([WHO, 2021](#)).

Diagnostics “aggregator” underfunded and lacks mandate to properly fulfill its role: The diagnostics landscape, like the therapeutics landscape, was more fragmented relative to the vaccine landscape. Unlike the therapeutics landscape, however, there was an institutional leader playing the role of an aggregator. FIND was essentially a CEPI-like equivalent for diagnostics, however it did not have anywhere near the same amounts of funding nor did it have the mandate to fulfill the diagnostics aggregator role fully. While this is partially due to the fact that diagnostics R&D and market are less

complex than those for vaccines and therapeutics, there will be a need for clearer and funded mandates in the diagnostics space for any future response.

WHO leadership challenges for pandemic diagnostics: It was noted that while WHO has dedicated expertise for vaccines, there is no dedicated center of energy or guidance for diagnostics (nor for therapeutics), which was seen to be a hindrance for partners working in these areas with WHO.

Supply/product bias of the ACT-A model: As noted in the therapeutics chapter, while the ACT-A has been a remarkable mechanism for promoting collaboration between entities, there may not have been enough focus on end-to-end solutions (e.g., how to run a testing and surveillance programme), which has become more of a challenge further downstream. Selected interviewees noted there was likely too much focus on specific products.

Lessons Learned

Governance/Institutional arrangements

- **Demand- and strategy-driven platform.** The pre-negotiated system for future outbreaks needs to have stronger technical leadership, with a fully funded mandate and clear views on testing strategy and how to navigate R&D, manufacturing and procurement. FIND is well placed to provide this leadership.
- **Better LMIC participation.** Voices from low- and middle-income countries, CSOs and communities must be integrated, and done so earlier. While the Diagnostics Pillar took the lead in the ACT-A as far as engaging with civil society and low- and middle-income countries, there were challenges. For example, Africa CDC took leadership of one of the four workstreams from the start, but was not sufficiently resourced to contribute significantly given the huge pressure they were under for their work in the region. Ensuring low- and middle-income country voices are well represented, supported and able to effectively engage is critical.

Financing

- **Integrated and strategic resource mobilization and allocation.** As noted in the therapeutics chapter above, the fragmented financing platform and fundraising efforts by the vaccines, therapeutics, and diagnostics pillars within the ACT-A led to competition between the three product areas and resulted in financing skewed towards vaccines. More strategic and integrated resource mobilization and optimal allocation through an integrated platform could improve the allocation of limited funding. As suggested in the vaccines chapter, upfront predictable funding outside ODA is needed to better prepare for future pandemics.
- **The principle of staged-funding (e.g., secure funding for diagnostics first within an end-to-end fundraising framework)** was also suggested to address the dearth of funding for therapeutics and diagnostics (and other essential supplies) relative to vaccines.

(2) Research and Development (R&D)

What Worked So Far

Diagnostic Innovation: As described above, the world had manual RT-PCR tests within a few weeks of the SARS-CoV-2 pathogen being identified, automated (high volume) RT-PCR tests by late April 2020, and the first Ag-RDTs meeting WHO performance criteria by September 2020. Moreover, the Diagnostics Pillar ensured that the automated RT-PCR and WHO-approved Ag-RDTs were made available in low- and middle-income countries in the same month in which they became available in HICs (albeit at low volume).

Independent Evaluation: FIND helped chase the epidemic with rapid initiation of evaluation of RDT studies in various countries. These sets of independent data provide further support of performance of RDTs and facilitate early adoption/procurement of these tests.

Challenges

Regulation, quality assurance, and evaluation: With so many diagnostics of varying quality on the market, critical aspects to gauge include regulation, quality assurance and evaluation. Interviewees noted that R&D around diagnostics has been a “complete wild west” with little oversight and many poor-quality tests. In some instances countries who ordered tests had to throw them away. In combination with a lack of diagnostics literacy at the country level and in governments, this points to a need for greater regulatory focus for diagnostics. There is also a need for independent evaluation that compares diagnostics, backed by transparent and standardized protocols. While FIND provided some of this, the first wave of the pandemic had already ended, limiting utility.

Variants: As noted in the therapeutics chapter, the emergence of variants is of increasing concern, with a clear incentive to scale-up testing and reduce prevalence of COVID-19. A lack of sequencing capacity has also made identification and tracking of new variants challenging.

Lessons Learned

Quality control for diagnostics: In the absence for now of independent evaluation for new diagnostics, countries need to establish quality control measures and cross-checking against “gold standard” molecular tests until formal evaluation data are available. Countries need to stay updated on the external validations performed by organizations such as WHO, the CDC, FIND, and collaborative research institutes ([MSH, 2020](#)). Having one standard protocol available would be useful at the global level with common approaches and frameworks for validating test design and performance (i.e., accuracy and reliability), regardless of whether there is an emergency. Going forward, there is a need for such a function to be carried out by a leading organization with the mandate, funding, and networks to support regional and national regulatory institutions on this. FIND offers such technology and support services for diagnostic solutions, especially for poverty-related diseases ([FIND, 2021](#)).

Surveillance and the role of diagnostics as prevention: The centrality of diagnostics for effective surveillance is critical as the first line of defense in a pandemic, and a necessary tool for prevention. Stronger surveillance networks and sequencing networks (especially given the potential of new variants) must be a priority. R&D for countermeasures to COVID-19 was considerably accelerated after sharing of sequences and once the regulatory environment was more permissive. Expanding surveillance and sequencing capacity in the future by scaling laboratories, data systems and training has been suggested.

(3) Manufacturing at Scale

Challenges

Geographic concentration: While manufacturing locations are heavily centered in the United States, more than 80% of US-manufactured diagnostics were initially reserved for HICs, leading to major bottlenecks globally. Respondents noted that China and East Asian markets, in particular, also developed their own tests. In addition to China, South Korea was highlighted as a major producer who was already in the space. While Chinese manual molecular tests were good, they were cumbersome to use and hard to implement in LMIC settings, so not very attractive from an equity standpoint. According to evaluations conducted by FIND, Chinese RDTs were generally of poor quality, which damaged their reputation in this space early on in the pandemic (especially on the immunoassay side).

It was noted that South Korea has been a strong partner with regard to industry partnerships, fair pricing, and tech transfer for rapid scale-up. South Korea-based SD Biosensor is one of the main providers of Ag-RDTs given its EUL from WHO, along with the Ag-RDT from Abbott and the most recent addition from India's PMC (discussed under achievements). For commercialized Ag-RDTs specifically (n=157), about half are from China, 24% from Europe (Switzerland, Germany, UK, etc.), and 11% from the United States and South Korea, respectively, in addition to other countries ([FIND, 2021](#)).

Lessons Learned

Production: Diversification of geographic production of diagnostics is needed.

Import/export restrictions: The export restrictions of one country are restrictions on imports of another. With the high degree of interdependence in trade in COVID-19 products, such measures can have wider impacts, including for low- and middle-income countries that rely on imports for COVID-19 goods. Reducing import barriers on COVID-19 products, even if temporarily, can help ([OECD, 2020](#)).

Small pool of manufacturers: As with other tools, reliance on a small number of countries with manufacturing capacity was also a challenge for diagnostics, pointing to a need for greater levels of local manufacturing.

(4) Procurement

What Worked So Far

The Diagnostics Consortium (which doubles as the supply workstream of the diagnostics pillar) has procured 65 million tests, including the majority of WHO-approved Ag-RDTs and automated PCR tests provided to Low- and middle-income countries (some big UMICs, including India, Indonesia, Brazil, and South Africa have bought their own).

Partnership to Accelerate COVID-19 Testing (PACT): Launched in April, 2020, PACT is an initiative to help prevent transmission and deaths, and to minimize the social and economic harm due to COVID-19. It seeks to implement well-coordinated actions and strong partnerships to strengthen the effectiveness of response across Africa ([African Union, 2020](#)). It has four goals: to scale up testing for COVID-19, to continue training healthcare workers on the continent, to establish a platform for pooled procurement at Africa CDC, and to deploy one million community workers who will help trace contacts of confirmed cases. It enabled Africa to increase the number of countries with testing capacity from two to 43 in three months and train thousands of lab workers ([Nkengasong, 2021](#)).

AMSP and AU emerged as important leaders in facilitating procurement and distribution of illumina platform and other diagnostic tests ([Africa CDC, 2020](#)): Public Health institutions in Africa have been implementing Next-Generation Sequencing (NGS) based surveillance to build a deeper understanding of endemic diseases and outbreaks. SARS-CoV-2 positive samples are currently sequenced by only a few African institutions to characterize circulating strains. Africa CDC is now expanding the network of institutions with NGS capabilities to empower additional countries to rapidly characterize outbreak samples, without the need to ship samples across borders. This will help spur the rapid and accurate identification of transmission pathways within and between populations and provide information on a probable source. Such tools will ensure African countries have robust and precise methods for identifying, comparing, and classifying pathogenic organisms in a timely manner, helping the continent better respond to current and future disease threats.

However, AMSP primarily served as a procurement platform for non-WHO-approved diagnostics and PPE from China, and so still has limited quality assurance and reporting capabilities that must be strengthened.

Challenges

Funding: As noted under governance, funding has been a challenge for the diagnostics pillar. Funding for procurement in particular has been one of the biggest bottlenecks.

Infodemic in procurement: The infodemic was not just a challenge for members of the public, but for governments trying to procure what they needed for effective pandemic response ([WHO, 2020](#), [UNDP, 2020](#)). Governments had to collate huge quantities of information from different sources, with no tools to differentiate between reliable and unreliable information and knowledge, even for high-level decision-making processes.

Reagents: Many countries are struggling with the supply of reagents and disruption across their laboratory system. This is of concern because not only does it affect the COVID-19 response, but it also impacts other disease programmes. This bottleneck in accessing diagnostics also extends to other laboratory commodities. Testing requires reliable supplies of a range of materials, including swabs, transport media, reagents, primers, assays, and PCR machines ([Rajan et. al., 2020](#)). Internal controls at the country level to assess additional sample collection materials and consumables required to perform tests, whether these need to be purchased separately from manufacturers or via other distributors, has been a capacity challenge ([MSH, 2020](#)).

Lessons Learned

Timely knowledge and information hub for countries: A reliable and agile knowledge and information hub with clear and timely guidelines is needed, not only for research, but also for procurement and best practices (e.g., to understand how other countries are dealing with common problems like access to reagents or machines; show transparent prices that countries should be paying; sources for products; etc.). This could be established either at regional and/or global levels.

Better access to supranational architectures for pooled procurement: While there are examples of effective regional procurement initiatives (e.g., AMSP), such mechanisms were not universally available. Key informants noted that some Latin American countries, for example, did not have the means to collectively procure supplies with other countries and benefit from economies of scale. Mechanisms put

in place prior to and during the pandemic and during did not work effectively in many instances with some countries noting they did not find a way to improve access to quality diagnostics.

Existing mechanisms should be leveraged, where possible. Countries have different mechanisms (e.g., revolving funds, strategic funds, contraceptive funds) already in place that they contribute funds to, are used to working with, and have legislative approvals for. In some cases countries have already made changes to their regulatory frameworks in order to put funds towards these mechanisms. There is a need to learn from these funds, and adapt them for use in emergencies. This may present a good opportunity to align mechanisms already put in place under the UN.

De-linkage of R&D costs from product pricing. Given significant public investment in R&D, there are reasonable expectations that affordability should not be a concern, and that there must be a requirement for a public return on those investments, including collaboration (e.g., tech transfer, patent pooling, IP sharing, etc.) over competition, affordability and equitable access. Pricing of the Astra Zeneca vaccine through COVAX reflected such an approach, however, such de-linkage approaches remain ad-hoc, fragmented and limited ([Bulc & Ramchandani, 2021](#)).

(5) Allocation

What Worked So Far

Allocation mechanism for diagnostics: An allocation mechanism is in place to enable the equitable allocation of diagnostics for low- and middle-income countries ([WHO, 2021](#)). The allocation principles were developed based on ethical principles of equity, transparency, consistency, inclusiveness, and accountability. Initial diagnostic volumes were calculated by country using a number of considerations, including the potential affected population, health system vulnerability and market access, existing instrument footprint, and country capacity. The epidemiological context of each country was not incorporated into the first calculated allocation because many low- and middle-income countries were unable to access tests and therefore unable to confirm cases to better understand their epidemic. The continuous deep engagement of countries on the allocation framework through regular WHO Member State consultations reinforces the urgency of this element and its relevance. WHO has communicated the total volumes available to countries through its country offices (Global Fund, 2020). Estimates are that sufficient supply is available to meet demand with the current available funding. For Ag-RDTs the funding constraint has outweighed the supply constraint. The Global Fund is making SARS-CoV-2 Ag RDTs available through the Global Fund's Pooled Procurement Mechanism under C19RM (Global Fund, 2021).

Countries received supplies through ACT-A, though not at adequate levels. India, for example, received support on primers and probes. They received US \$0.5 million tests to begin with, which was escalated to US \$1 million after that. This helped them weather the storm during the early stages of the pandemic.

Challenges

Ability for global mechanisms to accept/leverage approvals from multiple well-established regulatory authorities: To date, only three Ag-RDTs have been granted EUL by WHO. Since WHO EUL is a pre-requisite for a product to be provided through the ACT-A, the ability for any global mechanism like the ACT-A to accept/leverage approvals from more well-established regulatory authorities needs to be

considered. Relying only on WHO EUL approval alone can be a constraint on rapid deployment of new tools.

Evasion of allocation Frameworks. There were initial difficulties in ensuring that partners (and countries) adhered to a shared equitable allocation model. Some countries and agencies supporting countries engaged in bilateral deals in ways that undermined an equitable allocation approach. Manufacturers made incompatible promises to multiple agencies and countries.

Lessons Learned

Low case-counts due to limited diagnostic testing: Interviewees noted that it is a myth to say Africa was not hit hard by the pandemic. The true impact may not yet be known. Due to limited access to diagnostics, and therefore limited testing, “we are still flying blind in most of Africa”. For this reason, South Africa may not necessarily be the epicentre of the pandemic in Africa: it could be rather a reflection of higher testing rates compared with other African countries. Recent seroprevalence data from four states in Nigeria found that as many as 1 in 5 individuals in Lagos, Enugu and Nasarawa State had been infected with SARS-CoV-2 ([Ihekweazu & Salako, 2021](#)). These rates of infection are higher than those reported through the national surveillance system and reveal that the spread of infection in the states surveyed is wider than is obvious from surveillance activities.

Clear guidance on use cases is needed: As with therapeutics, use cases help drive demand. Demand and global allocation go hand-in-hand. Fair allocation does not happen automatically, and coordination is needed. The diagnostics pillar faced challenges around providing technical assistance around use cases (partly because of logistics, partly because the knowledge on this was developing in real time). There is a need for guidance on extended use cases outside of the health system as well (e.g., border crossings, schools, airport, etc.)

(6) Delivery

What Worked So Far

Leveraging health systems capacities: Multiple countries around the world are leveraging HIV and TB molecular testing capacity built up over many years to test for COVID-19. In West Africa, these same capacities contributed to the Ebola response ([WHO, 2020](#)). They were again leveraged during COVID-19, a testament to how investing in health systems pays dividends for health security. The DRC, for example, leveraged TB/GeneXpert capacity from the Ebola response.

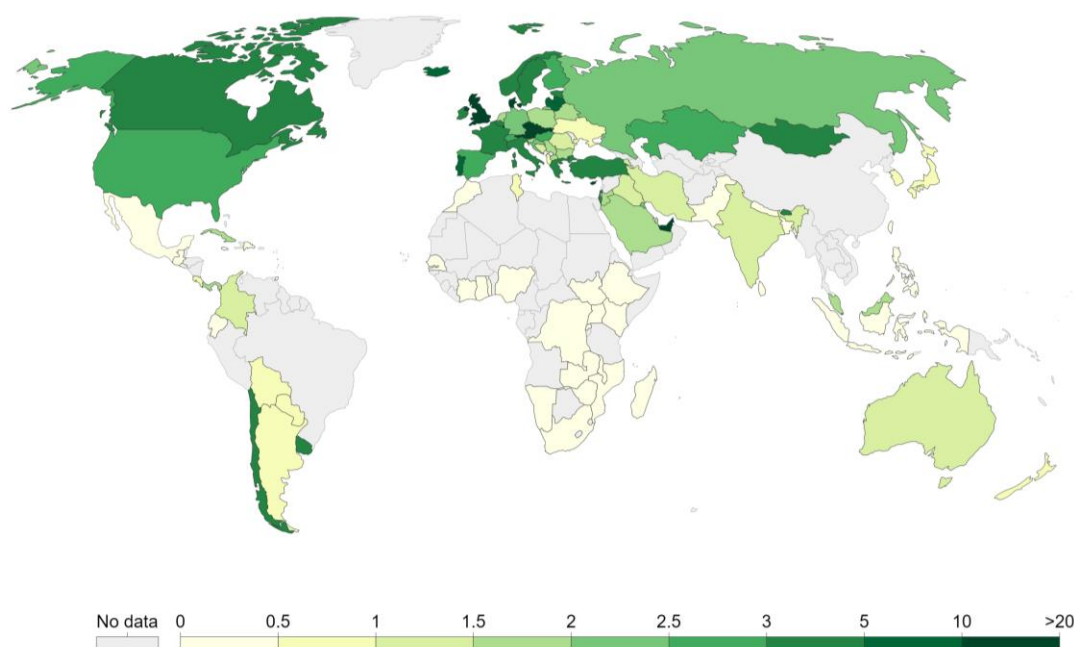
Implementation Checklist: Safe and effective implementation of SARS-CoV-2 Ag-RDT testing services involves several critical elements being in place. A national-level SARS-CoV-2 Ag-RDT implementation checklist was developed to serve as a practical ‘aide-mémoire’ for implementers to integrate Ag-RDT testing into their national response plans ([WHO, 2020](#)).

Challenges

Equity: Most countries still face major challenges in scaling up testing capacity, coupled with a lack of understanding of the different types of tests and how they can be used ([Peeling et al, 2021](#)). Few countries have managed to scale up testing capacity to gather sufficient population-level data to inform public health decisions on reopening of schools, return to work, mass gatherings, and travel, or to allow easing of other social restrictions ([Peeling et al, 2021](#)). Figure 15 shows the number of daily tests per

thousand people on April 23, 2021. Because the number of tests is often volatile from day to day, the figures show a seven-day rolling average.

Figure 15: Daily COVID-19 tests per thousand people, April 23, 2021



Source: [Our World Data](#)

WHO along with key stakeholders defined minimum performance specifications for point of care Ag-RDTs in a TPP ([WHO, 2020](#)), and as noted above, granted three with EULs. Despite these introductions, testing capacity remains highly centralized in many countries, and is often insufficient to meet the current demand. This is especially true in low- and middle-income countries, where fragile health systems and exclusive reliance on global supply chains have often left healthcare providers unable to access urgently-needed tests. While high-income countries are now conducting an average of 533 tests per 100,000 people each day, in lower-middle-income countries the rate is almost 15 times lower, at just 36 tests per 100,000 people, and lower still for low-income countries at 5.5 tests per 100,000⁹. These issues arise from a lack of access to the laboratories needed for processing more complex molecular tests. Populations who often live far from health centres and need rapid results want to avoid multiple journeys. In addition, although WHO has released interim guidance on use of Ag-RDTs featuring important considerations for implementation, there is limited experience with these tests in routine settings and specific implementation guidance for use of these new tests is lacking ([WHO, 2020](#)).

Lessons Learned

D. Agility in use of diagnostics. There is a need to be more agile and encourage countries to use tests for use cases beyond those prescribed by WHO. This includes finding effective ways to decentralize the use of tests, including in other sectors (e.g., border crossings, airports, educational institutions, etc.)

⁹ Median values of 7-day rolling averages in each income group. Data correct as at Feb 16, 2021, www.finddx.org/covid-19/test-tracker

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