Vaccines, therapeutics, and diagnostics for covid-19: redesigning systems to improve pandemic response

Rohit Ramchandani and colleagues propose a framework to ensure essential public health tools are fairly distributed in future pandemics

Vaccines, therapeutics, and diagnostics are key public health tools for controlling the covid-19 pandemic, yet many countries, particularly low and middle income countries (LMICs), have had inadequate access. Many have yet to determine, for example, when and where they will be getting their vaccines from, and only 3% of people in low income countries had received at least one dose by October 2021.1

The Access to COVID-19 Tools Accelerator (ACT-A) is a multilateral coordination mechanism set up to accelerate development, production, and equitable access to covid-19 tests, treatments, and vaccines globally. The concept brings together governments, scientists, businesses, civil society, philanthropists and global health organisations. Despite its bold vision, ACT-A has thus far fallen short of its expectations. Covax, the vaccines pillar of ACT-A, has been responsible for less than 6% of the 6.82 billion covid-19 vaccines administered as of October 2021.2 The first outstanding efficacious treatment to which ACT-A’s therapeutic pillar has contributed is molnupiravir, which was shown to reduce the risk of hospital admission or death in October 2021.4 Oxygen therapy, still one of the best treatments available for severe cases, initially struggled from a lack of strategic prioritisation despite its critical importance. Testing did receive political attention but has been a bottleneck in many countries.5

Value chain analysis
We used a value chain framework to analyse the successes, challenges and lessons for key covid-19 tools (table 1).6 A value chain is a business model that describes the full range of interdependent activities needed to bring a product from conception to end user.6 It can be thought of as an ecosystem of players, processes, information, and resources required to effectively deliver a product.11 Aspects of the value chain considered included overall governance and coordination, research and development, manufacturing at scale, procurement, allocation and delivery.

Governance and coordination
While ACT-A shows unprecedented collaboration among key institutions, it has been perceived by some countries and civil society organisations as being too supply driven without enough focus on inclusivity and transparency. A lack of engagement with China, Russia, and many other LMICs, as well as delayed participation from the US government, limited the scope and acceptance of ACT-A as a global mechanism. The mechanism established itself during the emergency, in a stepwise fashion. The process was based on a standard market model—that is, development, trials, emergency use authorisation, selling to high income countries, then redistributing to LMICs—rather than with an “end-to-end” view whereby equitable access is considered from the beginning—during product design and allocation, research and development, manufacturing, and procurement processes. It relied on the decision making mechanisms of existing organisations, which some perceive as being overly donor-driven.13

Shared vision and industry policy
Stakeholders have not had a shared vision that the measures needed to control pandemics should be considered as part of a “global health commons,” available for all countries to ensure collective protection. A global health commons builds on the concept of a commons as managed pooled public access to certain property rights as well as access to goods and services that are valuable but in constrained supply.

The technologies to produce vaccines, diagnostics, and therapeutics are critical public health interventions to respond to international public health crises such as pandemics. Global common access to such technologies recognises this importance and the need for intervention to ensure equitable public access. Global health commons for vaccines have historically given rise to concerns about “free riders”—individuals benefiting from the commons through herd immunity of others’ vaccination while avoiding any potential costs of vaccination. However, a global health commons approach—recentring public health solidarity over corporate interests—has the potential to alleviate factors contributing to vaccine hesitancy or resistance.

Without this shared vision, and given the urgency in which decisions had to be made, the usual market based approach was taken. Global corporations developed and sold proprietary products designed for wealthy countries, leaving the rest of the world reliant on the goodwill of donors, development assistance, and charity. This is despite the substantial public investment...
before and during the pandemic in research, advanced purchases, liability waivers, and the logistics and delivery of vaccinations. In this respect, a shift to a global health commons for pandemic countermeasures seeks to realign public investment with direct common public benefit.

Financing
Insufficient and delayed financing is 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 type. Covax was unable to compete with high income nations with greater purchasing power or hosting big manufacturers. The funding shortage has been even more serious for therapeutics and diagnostics. For example, the ACT-A diagnostics pillar was unable to use a volume guarantee it secured for quality antigen rapid diagnostic tests because of lack of funding.

Research and development
No end-to-end strategy
Although the development of vaccines has been an extraordinary success, the global effort by Covax to make them available across populations had no clear global strategy. For example, research efforts were focused on making vaccines available as fast as possible rather than on adherence to target product profiles that consider use in LMICs (such as not requiring ultra-cold chain handling).

The lack of a clear strategy to guide research and manufacturing also applies to diagnostic tests. The development and use of target product profiles could have established the type of tests wanted, including specifications for sensitivity and specificity, early on.

Weak trials with excessive focus on speed
Weak capacity and coordination of clinical trials—including a lack of well distributed regional trial sites, the absence of trials directly comparing effectiveness of currently available vaccines, and poor integration of therapeutic research pipelines into trials—has resulted in many poor quality trials with limited actionable findings.

Vaccine developers selected specific and differing endpoints for their initial trials, which in some cases facilitated faster registration. They were conducted in selected populations with limited numbers of participants in high risk groups such as elderly people and those with serious underlying medical conditions. Until at least October 2020, none of the trials was 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. Also, as the vaccines were researched in an extremely short space of time, safety could not be assessed reliably. While regulators around the world changed processes to speed research and regulatory pathways, many opportunities were missed for integration of improved public health criteria in selection of endpoints and, more generally, for greater efficiencies, better use of tools, improved data sharing, and more coordinated approaches.

Financing and institutional leadership
Financing and support by the US Biomedical Advanced Research and Development

### Table 1 | Successes and challenges across the value chain for covid-19 tools

<table>
<thead>
<tr>
<th>Successes</th>
<th>Challenges</th>
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<tr>
<td>Overall governance and coordination</td>
<td>• ACT-A demonstrates an unprecedented collaboration by multilateral agencies and the private sector&lt;br&gt; • WHO focus on coordination and norms</td>
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<tr>
<td>Research and development</td>
<td>• &gt;102 vaccine candidates in clinical testing, with 20 approved for use by at least one national regulatory authority in under 2 years (conventional vaccine development averages 8-10 years between discovery and licensure)&lt;br&gt; • Funds/capacity of Biomedical Advanced Research and Development Authority (BARDA)&lt;br&gt; • Innovation financing by China, Russia, India, etc&lt;br&gt; • Pre-investments for “disease X”&lt;br&gt; • Coalition for Epidemic Preparedness Innovations (CEPI) already set up and triggered rapid funding to secure doses</td>
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<tr>
<td>Manufacturing at scale</td>
<td>• BARDA, European, Chinese, Russian financing&lt;br&gt; • CEPI financed $600-$700m by stepping up beyond its original mandate&lt;br&gt; • Strong manufacturing capability in India, etc&lt;br&gt; • Some local production agreements (Brazil, India)</td>
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<tr>
<td>Procurement</td>
<td>• 4.69 billion doses secured (or optioned or received as donation) by Covax&lt;br&gt; • Regional procurement happening in LMICs (eg, by African Union, PAHO for Latin America and Caribbean, etc)&lt;br&gt; • World Bank stepped up to fund vaccines and delivery (up to $20bn)</td>
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<tr>
<td>Allocation and delivery</td>
<td>• Established allocation and dose sharing principles&lt;br&gt; • 2 new bodies (Independent Allocation of Vaccines Group (IAVG) and Joint Allocation Taskforce (JAT)) involved in allocation of Covax Facility vaccines</td>
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| | • Lack of up front (or follow-up) at-scale pooled funding to finance R&D and secure doses for LMICs<br> • Ecosystem gaps in getting virus samples, curating genetic sequences, developing animal models<br> • Lack of data sharing rules (e.g., non-transparent clinical trial results)<br> • Unclear vaccination strategy/product specifications to link research to delivery<br> • Clinical trials designed for rapid approval and not to answer key public health questions<br> • Mainly supply driven<br> • Western biased, led by a few donors; few LMIC and civil society voices<br> • Lack of intellectual property sharing and technology transfer which could help address artificial scarcity of vaccines<br> • C-TAP and WHO vaccine technology transfer hub have not been used<br> • Gap between CEPI/GAVI mandates—financing at risk manufacturing<br> • Serious shortages and geographic concentration of manufacturing capacity with very limited capacity in Africa and Latin America<br> • Lack of expertise in, and transparency to support, price negotiation in LMICs<br> • New challenges—supply chain, dual shot, emerging variants because of inadequate vaccination coverage, infodemic, and hesitancy<br> • Inadequate and unequal investment in public health infrastructure and rollout readiness<br> • Slow disbursement of committed World Bank funds<br> • Only 3% of people in LMICs had received at least one dose by 21 October 2021 |

<sup>8</sup> BMJ 2021;375:e067488 BMJ: first published as 10.1136/bmj-2021-067488 on 28 November 2021. Downloaded from http://www.bmj.com/
Authority (BARDA) and the Coalition for Epidemic Preparedness Innovations (CEPI), as well as past scientific investments contributed substantially to the successful development of vaccines. However, high income countries directly funded vaccine development to help secure supply for themselves, which weakened CEPI’s and Covax’s ability to negotiate with manufacturers. By contrast, therapeutics have suffered from lack of a leading institution like CEPI as well as structural underinvestment, and the diagnostics pillar has also been significantly underfunded.

**WHO’s role**

WHO’s research and development blueprint served to establish a common research agenda quickly. It was most effective in supporting vaccine product development and to a lesser extent for diagnostics. Despite the success of the Solidarity trial for therapeutics, the experts we interviewed from other international institutions and non-governmental organisations considered management of clinical research programmes should not be part of WHO’s purview as this can create conflicts of interest given WHO’s role in approving products based on trial results.

**Manufacturing**

Manufacturing shortages and geographical concentration of manufacturing capacity have been a key challenge. Limited transfer of technology and patent licensing have been central to these geographical limitations. Platforms and tools to enable technology transfer, such as the covid-19 technology access pool (C-TAP) and the WHO vaccine technology transfer hub have not been effectively used. The intellectual property right TRIPS waiver proposed by South Africa and India was not supported by several high income countries.

No agency is mandated to finance and strengthen manufacturing capacity for vaccines, therapeutics, and diagnostics. Expanding regional capacity for key platform technologies (eg, monoclonal antibodies and mRNA) to avoid reliance on few manufacturers and fortify supply systems should be a priority. It requires transfer of highly specific and specialised technology and know-how, in coordination with regulatory oversight, robust participation of vaccine developers, and application of good, consistent, laboratory biological manufacturing practices, and addressing financial sustainability of such facilities. Given the large challenges, a strong system is required to accelerate progress.

**Procurement**

Roles and responsibilities of global institutions in procuring covid-19 tools have been unclear, and regional institutions have emerged as an important procurement mechanism (box 1). There were also challenges in procuring raw materials and reagents necessary to implement vaccinations and diagnostics.

**Allocation and delivery**

In addition to the inequities highlighted above, countries say that they are receiving information on vaccine allocation without knowing when doses will arrive. This makes the planning of vaccination extremely difficult and slows down the preparation for vaccinations, including the use of funds from the World Bank and other institutions. This is increasing the risk of countries not being prepared when large quantities of doses arrive in late 2021 and across 2022, as planned by Covax and other sources.

The strategic phases and current allocation mechanism for Covax establishes two phases of vaccine allocation to recipients. Phase 1 consists of the proportional allocation of 20% of the population until all countries are covered to this level. This was intended to end the acute phase of the pandemic by securing enough doses to ensure health workers, elderly people, and vulnerable groups were protected by the end of 2021. Phase 2 will take a more epidemiological approach, consisting of weighted allocation dependent on the proportional coverage requested by countries and consideration of vulnerability and covid-19 threat. Flexibility tailored to epidemiology in allocation of vaccines, therapeutics, and diagnostics is critical but requires sophisticated country level data collection and flows.

LMICs, particularly in Africa, are experiencing substantial difficulties with distribution, administration, and uptake (including from vaccine hesitancy). This highlights the importance of preparedness and systems building outside emergencies. High level political dialogues on vaccine supply and deployment have not taken place at global level despite their critical importance.

**Proposed framework for future mobilisation of pandemic tools**

Lessons from ACT-A can guide the establishment of a permanent platform that stands in readiness for future pandemic responses. We propose a framework that highlights five key elements of a pre-negotiated system that would accelerate research and increase the likelihood of equitable access under a global health commons (fig 1).

**End-to-end research and development platform**

The current supply driven research and development process needs to shift towards more of an end-to-end process in which initial research, clinical trials, manufacturing, and procurement are guided by a goal and strategy of equitable and effective access to a global health commons. Box 2 highlights two important examples.

**New industry policies and country agreements**

At the vaccines roundtable conducted as part of the work of the Independent Panel on Pandemic Preparedness and Response, there was consensus that the international covid-19 response failed to direct industry towards equitable access and effective use of vaccines in the face of vaccine nationalism and profiteering. The same problem could arise with treatments for covid-19 and in future pandemics. Systems need to incorporate rules and industrial policies to deliberately govern the collaboration between public and private sectors (box 3). The proposed pandemic treaty should provide a platform for such rules and policies. This must cover incentives and financing, and clarify roles, responsibilities, and liabilities.

**Operating through regional platforms**

The future pre-negotiated system should shift to trials, manufacturing, procurement, and country coordination and collaboration through decentralised regional platforms. High income countries and emerging economies are investing in vaccine manufacturing capacity in response to the covid-19 pandemic. Regional networks should be created by piggybacking on such investments to secure a portion of manufacturing capacity for a global response mechanism and aggregate global manufacturing capacity.

The new global mechanism must also support the strengthening of the manufacturing capacity in LMICs. For example, African Union and Africa Centres for Disease Control and Prevention established the Partnership for African Vaccine Manufacturing. They call for mRNA platforms for vaccines in Africa and aim to establish at least five regional vaccine production hubs as well as fill and finish capacities. Difficult challenges ahead include aggregating reliable demand to meet competitive economies
Regional institutions have emerged as important for pooled procurement and negotiation, information sharing, technical assistance, and rapid response to country needs. The Africa CDC and Africa Union’s AVATT (Africa Vaccine Acquisition Task Team), for example, exemplified these functions. There are strong country demands for such regional capacity as many countries, particularly low and middle income countries, do not have access to technical and market expertise and reliable information to use when negotiating with manufacturers. In some instances, governments have been asked to put sovereign assets such as embassy buildings, military bases, or federal bank reserves as guarantees against the cost of future legal cases.\textsuperscript{20,21} Regional capacity to effectively negotiate these proposals and the like, has been lacking in Asia and there is room for further strengthening in Africa and Latin America. Such capacity could alleviate some of the serious inequities in procurement and manufacturing challenges.

Gavi, the Vaccine Alliance, has had a critical 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 helping to fill this gap, deploying $1bn through its covid-19 response mechanism. It also secured substantial new funding ($3.7bn) to help meet procurement needs. But clarity in institutional leadership and strengthening of expertise are required for future pandemics.

The World Bank funded country procurement of scarce commodities with a funding commitment of $6bn for initial response and $20bn for vaccine response. At the same time ACT-A pillars tried to centralise procurement with equitable distribution. This created competition between the two, and the lack of coordination hindered response efforts. Further clarity on the roles of the World Bank and other development banks, including potential reforms of their funding approach are needed. This will require an objective assessment of the bank’s support for covid-19 responses including a review of options for it to finance global public goods.

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 is advanced in building some of these systems and capacities, and similar mechanisms and capacity are needed in other regions.

Clinical trial sites need to be well distributed, including in LMICs. The future global mechanism should work with regional institutions to map out, strengthen, and track the potential research network. This could also provide critical research capacity for other public health purposes (eg, poverty related and neglected tropical diseases) outside pandemics.

Inclusive governance with a clear playbook
The current system needs to be reshaped to include representation from low and middle income countries, civil society organisations, countries with relevant manufacturers (such as China, Russia, and India), high income countries, and private manufacturers. It also requires effective ways of communicating with stakeholders to ensure all voices are heard. The new mechanism should also establish a much clearer playbook with deliberate strengthening of key institutions to address critical gaps across the whole value chain (eg, research into therapeutics, at-risk manufacturing across all products, procurement for therapeutics and diagnostics, oxygen, protective equipment) as well as better integration of the World Bank and regional institutions and more focused roles for WHO.

Predictable financing
Equipping a new global mechanism with substantial upfront funds to counter nationalism and enable rapid response, as well as strengthening global manufacturing capacity and meeting other financing needs for pandemic preparedness, requires fund-
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Box 2: Examples of end-to-end research process

Strategy-led portfolio approach
The independent prioritisation and simultaneous development of multiple product candidates is carried out in alignment with country demand, clear testing, treatment, and vaccination strategies, as well as target product profiles.23 This minimises risks associated with product failures and facilitates a greater number of appropriate products for all settings, in particular for low and middle income countries (eg, those with easier routes of administration and storage). WHO’s research blueprint for covid-19 and the coordinated global research roadmap should be developed and used further.

Clinical trials guided by public health questions
Clinical trials should answer the right public health questions based on high quality, standardised protocols rather than being focused on obtaining regulatory approval. Trials should directly compare products. This requires effective central coordination across trials; prioritising what candidates to test; managing partnerships with regulators and manufacturers; and making data transparent through a data sharing hub.

Box 3: Key elements of the industry policies and country agreements

- **Pre-negotiated contracts**—As part of the new global mechanism, pre-negotiate legally binding contracts for pandemic emergencies with key manufacturers, based on an agreed trigger. The contracts could include one-off or real time manufacturing capacity for diagnostics, therapeutics, or vaccines for the global mechanism and provision of voluntary intellectual property licences and technology transfer to generic manufacturers. This will be subject to predefined terms including adequate remuneration.

- **Reshape Covax as a truly global approach to influence industry with country agreements**—Greater funding and more participation in Covax from high income countries before or at the start of future pandemics would enable it to secure more vaccine doses and better terms for the world (eg, volume guarantees, manufacturing capacity, favourable pricing). Agreements under the pre-negotiated system would need to include countries’ commitments or obligations to obtain diagnostics, therapeutics, and vaccines from the global mechanism and limit bilateral deals with manufacturers through a framework convention for pandemics.

two roundtable discussions—one on vaccines, and the other on therapeutics and diagnostics—with 18 experts. RR and SM conceived and designed the manuscript. RR and SM drafted the manuscript with inputs from all authors. All authors contributed to revising the manuscript and approved the final version.

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Rohit Ramchandani, professor1,2,3
Michel Kazatchkine, panel member4
Joanne Liu, panel member5,6
Preeti Sudhan, panel member7
Mark Dybul, panel member7
Precious Matsoso, panel member8
Anders Nordström, head of secretariat6
Alexandra Phelan, panel secretariat member9
Helena Legido-Quigley, associate professor10
Sudhir Singh, panel secretariat member10
Shunsuke Mabuchi, panel secretariat member11,12

1Antara Global Health Advisors, Toronto, Canada
2Johns Hopkins University Bloomberg School of Public Health, Baltimore, USA
3University of Waterloo School of Public Health Sciences, Waterloo, Canada
4Balsilie School of International Affairs, Waterloo, Canada
5Independent Panel for Pandemic Preparedness and Response
6McGill University’s School of Population and Global Health, Montreal, Canada
7Georgetown University, USA
8Independent Panel for Pandemic Preparedness and Response Secretariat
9Saw Swee Hock School of Public Health, National University of Singapore, Singapore
10Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
11Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK
Correspondence to: S Mabuchi shunsuke.mabuchi@gmail.com

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