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A new era for vaccine innovation

Harnessing the lessons learned from COVID-19

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Harnessing the lessons learned from COVID-19

WISH 2022 Forum on Vaccine Innovation

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FOREWORD

Governments around the world have employed disparate strategies – ranging from near total lockdowns to more laissez-faire regulations – to combat the COVID-19 pandemic. While the benefits and drawbacks of these approaches provoke heated debate among policymakers and the general public alike, one thing is clear: widespread vaccination is the most effective weapon in the fight against COVID-19.

The development and emergency-use approval of not just one, but several vaccines in a matter of months are stunning feats that have prevented millions of deaths and hospitalizations while averting hundreds of billions of dollars in healthcare costs worldwide.[1] Yet despite this success, the production, allocation and deployment of COVID-19 vaccines has been far from perfect, with many low- and middle-income countries still struggling to vaccinate even a fraction of their populations.

As we continue into the third year of this pandemic, it is essential that we take stock of what we've learned thus far in order to prepare for future threats. This report examines three main areas: the factors, enablers, and challenges of COVID-19 vaccine development; issues of access, equity and justice in vaccines and vaccination; and how lessons learned from COVID-19 vaccine development, production and deployment can be applied to other diseases. It concludes with a number of recommendations to build effective vaccine ecosystems to tackle future infectious disease challenges in a spirit of equity and justice.

Implementing this guidance will ensure that wider society benefits fully from scientific advances in vaccine development, preventing countless deaths and unnecessary illness around the globe.

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SECTION 1. FACTORS, ENABLERS AND CHALLENGES FOR COVID-19 VACCINE DEVELOPMENT

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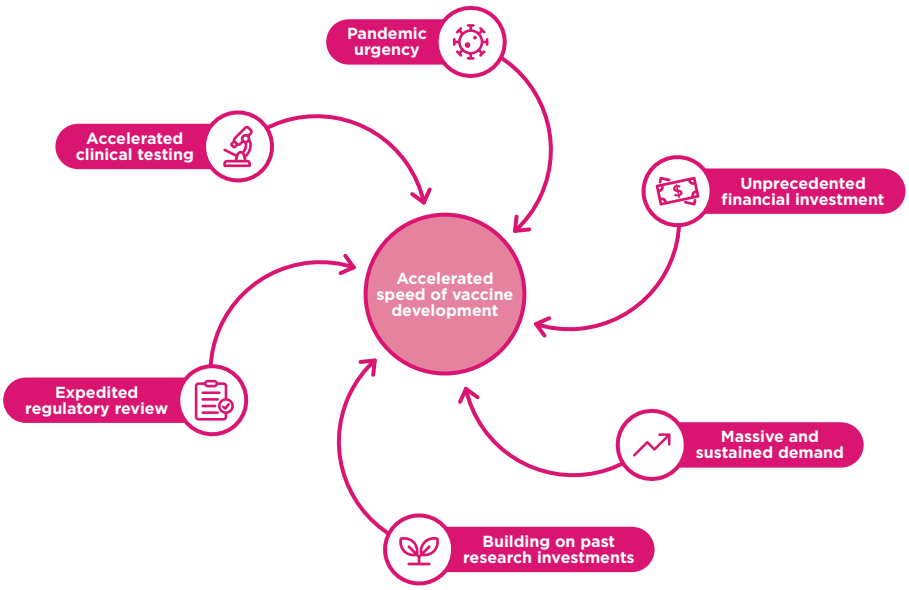
Vaccines are among the most cost-effective public health interventions currently available. Together with antibiotics and clean water, vaccination against infection and disease has saved millions of lives and increased life expectancy in all countries.[2,3] The discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[4] and the global COVID-19 pandemic[5] were rapidly followed by unprecedented multinational efforts to develop vaccines to prevent infection and severe disease, turn the pandemic tide, and mitigate the devastating economic and societal damages associated with the virus.[6]

Clinical development and approval of vaccines typically takes five to 10 years and only 10 percent of vaccine candidates receive market authorization.[7,8] However, the COVID-19 pandemic overcame many of these historical challenges, and within 12 months of the detection of the first SARS-CoV-2 case, at least six vaccines had received emergency use authorization. As of December 2021, just two years following the detection of the first SARS-CoV-2 case, 36 vaccines[9] had been approved by at least one country.[10] Identifying and understanding the impact of the different factors that enabled the rapid clinical development and emergency use authorization of COVID-19 vaccines may shed light on lessons learned to streamline future vaccine development for pandemics, epidemics of emerging pathogens, and endemic diseases.[11–13]

Factors impacting on vaccine development and authorization timelines

Several factors increased the speed of vaccine development: pandemic urgency; unprecedented financial investment; massive and sustained demand; building on past research investments; expedited regulatory review; and accelerated clinical testing. Scale-up and 'manufacturing at risk' – when pharmaceutical companies begin mass-producing vaccines at the same time as clinical trials rather than waiting for regulatory approval – are important accelerators of vaccine availability, and also a significant financial risk because large investments need to be made before safety and efficacy are demonstrated.

Figure 1. Factors accelerating the speed of vaccine development



Pandemic urgency

The COVID-19 pandemic had significant health, economic, and social impacts worldwide. The full impact of the pandemic has been much greater than what is indicated by reported deaths due to COVID-19 alone. Although reported COVID-19 deaths between 1 January 2020 and 31 December 2021 reached almost 6 million worldwide, recent estimates suggest instead that the true number may be between 15.9 and 18.2 million (measured by excess mortality).[14] The clinical impact of COVID-19 goes further than the acute respiratory distress and deaths to a range of chronic secondary effects (or *sequelae*) that delay recovery and have a marked influence on daily functionality in large numbers of patients.

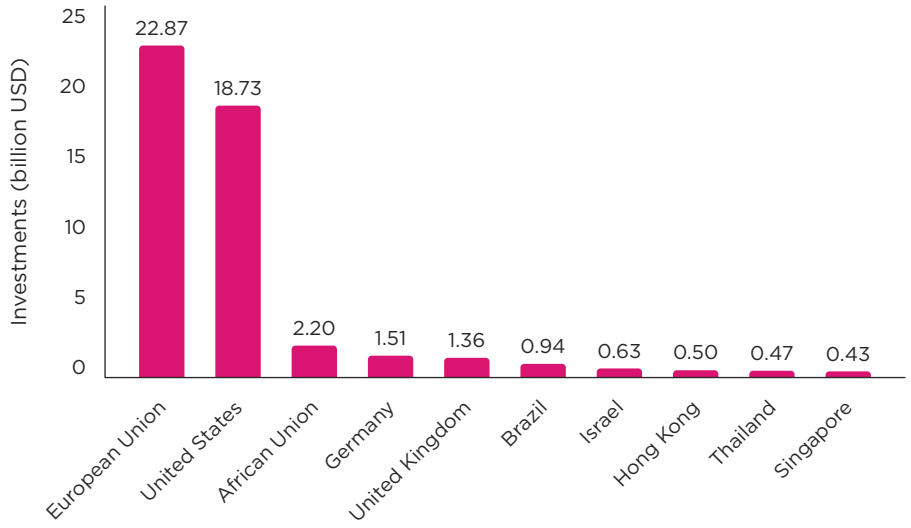
The increasing number of lockdown days, monetary policy decisions and international travel restrictions severely affected the level of economic activities and major stock market indices. Economic disruption also led to a significant increase in global inflation, unemployment and energy supply issues.[15] The International Monetary Fund stated in March 2020 that it expected a global recession that would be at least as bad as the 2007/08 global financial crisis.[16] Lockdowns heavily impacted on daily life and increased inequities; they had negative effects on educational outcomes, mental health and domestic violence.[17,18]

Taken together, these factors had a significant impact on key stakeholders' considerations regarding timelines for vaccine development and authorization. High levels of political will and a sense of global vulnerability and urgency create a supportive context for partnerships and

collaboration, with a sense and necessity of openness to share research outputs, improve vaccine design, accelerate clinical development and expedite access.

Unprecedented financial investment

Figure 2. COVID-19 research & development and advance purchase agreements investments by country, as of July 2021*



* Includes investments made by public and private sectors, philanthropic and other funders in COVID-19 R&D, either directly or to intermediaries (such as CEPI), and through APAs (signed before vaccine approval). The figure does not include the pharmaceutical industry's own investment. Figure shows top 10 countries/blocs with greatest investment, based on publicly available sources.

Source: Global Health Centre. 2021. COVID-19 Vaccines R&D Investments. Graduate Institute of International and Development Studies.[19]

Worldwide, more than $52 billion was invested in COVID-19 vaccine research and development (R&D) and advance purchase agreements (APAs) (see Figure 2), including more than $18 billion from the US Government Operation Warp Speed (an interagency program including different departments, the Biomedical Advanced Research and Development Authority, and private firms), and $1.53 billion from the Coalition for Epidemic Preparedness Innovations (CEPI).[20] These massive investments de-risk COVID-19 vaccine clinical development. APAs between governments and pharmaceutical companies provided a safety net for COVID-19 vaccine development, as financial burden and risk of failure were shared among multiple stakeholders. Investments were also made in manufacturing and key inputs such as vials and syringes to help improve success in the large challenge of scale-up.[21] Of note, much of the manufacturing investment was done 'at risk' during the clinical trials.

Additionally, as of May 2022, the World Bank has dedicated more than $8.7 billion to support vaccine purchasing and roll-out in over 74 countries.[22]

Massive and sustained demand

The unprecedented level of demand for COVID-19 vaccines emerged in the absence of other pharmaceutical interventions. One of the reasons for the massive demand was that many wealthy countries had placed advance orders and paid deposits for vaccine quantities far exceeding their needs. This led to pooling and co-ordination of funding to support vaccine development and the creation of an attractive global market for approved vaccines. COVID-19 Vaccines Global Access (COVAX) – the collaboration led by Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness (CEPI) and the World Health Organization (WHO), and the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator – is a groundbreaking global collaboration among governments, global health organizations, manufacturers, scientists, the private sector, and philanthropy to accelerate the development, production and equitable access to COVID-19 tests, treatments and vaccines. The early engagement and financing provided by organizations focused on emergencies played a key role in accelerating timelines for clinical development and removing some of the initial barriers faced by vaccine developers. This accelerated development by allowing clinical R&D activities to be conducted in parallel rather than sequentially. Of note, the academic sector has played a critical and cost-effective role for both pre-clinical work and clinical development.[23]

Expedited regulatory review

Regulatory authorities in countries of origin adopted a proactive approach to rapidly set minimum clinical, non-clinical and manufacturing data requirements to enable emergency use authorization for rapid access of safe and effective vaccines. Early and iterative guidance consultations between manufacturers and regulators expedited timelines. Regulators also prioritized COVID-19 reviews over non-COVID-related health products and allowed greater flexibility in the sequence of submission and rolling reviews. Through the European Medicines Agency's rolling review process, COVID-19 vaccines were approved in record times, ranging from 17 to 36 days.[24] However, it is important to note that regulators' prioritization of COVID-19 interventions had a negative impact on interventions for other diseases during the pandemic.[25–27]

The WHO Emergency Use Listing (EUL) is a risk-based procedure[28] for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics, with the ultimate aim of expediting the availability of these products to people affected by a public health emergency. WHO EUL was a prerequisite to the deployment of vaccines through COVAX, and for many countries that expedited their own regulatory approval to import and administer COVID-19 vaccines.[29]

Of note, several vaccines were being used before WHO EUL. The Sinovac vaccine first acquired emergency use authorization in China in August 2020, soon followed by Indonesia, Turkey and Brazil. China's National Medical Products Administration granted conditional marketing authorization in February 2021, followed by WHO EUL five months later in July 2021. The Sinopharm-Beijing vaccine received emergency use authorization in the United Arab Emirates in September 2020, then full approval in early December, followed by conditional market authorization in December 2020, and WHO EUL five months later in May 2021.[30] Similarly, AstraZeneca's COVID-19 vaccine was granted emergency use authorization in India as well as Argentina, the Dominican Republic, El Salvador, Mexico and Morocco for the active immunization of adults in January 2021, before WHO EUL.[31]

Building on past research investments

Decades of prior research performed to develop new vaccine platform technologies – for example, messenger RNA (mRNA)[32–34] and non-replicating viral vectors[35–38] – and the prior R&D activities on coronaviruses with pandemic or epidemic potential – for example, SARS-CoV-1[39] and Middle East Respiratory Syndrome (MERS)[40] – provided platforms and prior scientific know-how, enabling development of COVID-19 vaccine candidates for pre-clinical and clinical testing. Further, structure-based design, pioneered with HIV and Rous sarcoma virus (RSV) glycoproteins, informed the structure of MERS and SARS-CoV-2 spike glycoproteins. These were rapidly leveraged for COVID-19 vaccine development, and the prior research and vaccine development activities due to the SARS-CoV-1 and MERS outbreaks provided vaccine developers with a better understanding of the SARS-CoV-2 structural biology, mode of transmission, and areas of the virus to target for a strong immune response (the spike protein was used in all mRNA and viral-vectored vaccines). The US National Institutes of Health used a significant investment in HIV therapeutic and preventive trials networks to allow more rapid enrolment of volunteers in clinical trials.

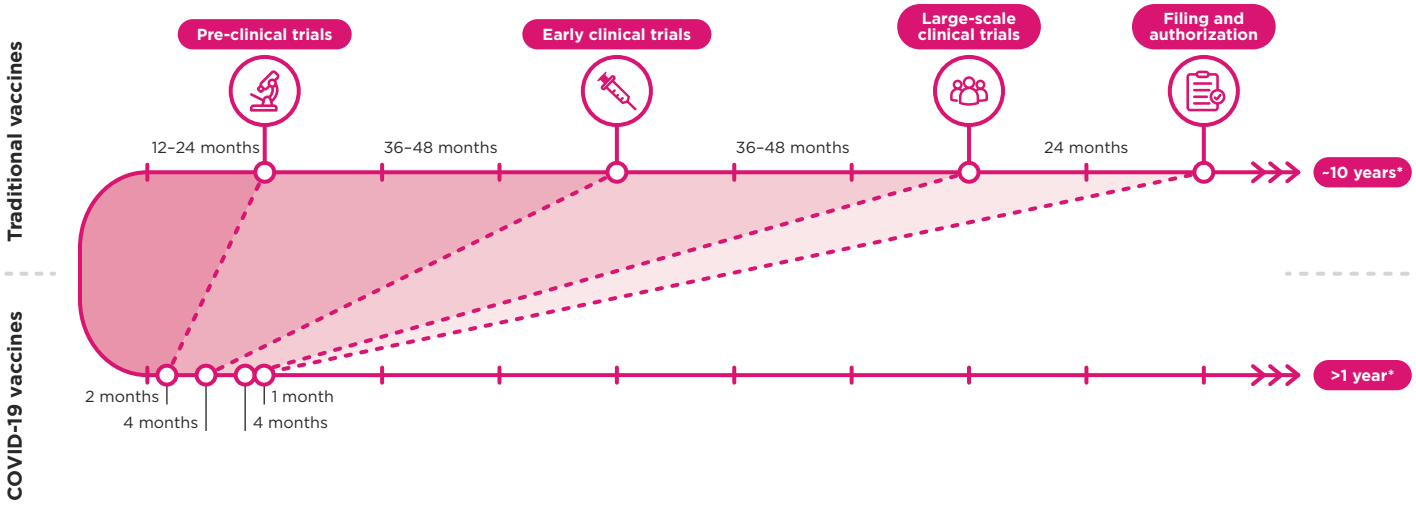
Accelerated clinical testing

The development of several safe and efficacious COVID-19 vaccines occurred in 12 months rather than five to 10 years.[41] Rather than the systematic, iterative and sequential progression of clinical trials for typical vaccines, clinical trials of COVID-19 vaccines were telescoped – with initiation of the next phase of clinical development once adequate safety and critical path immunogenicity signals were obtained and appropriate

adjustments in dose or schedule were made. As noted above, the availability of well-trained clinical networks allowed the US to rapidly enroll volunteers in clinical trials. Rapid response platforms were used to great effect: mRNA, viral-vectored, and whole inactivated virus (WIV) vaccines have been developed and manufactured rapidly compared to other technologies, such as subunit and live attenuated vaccines, that had greater manufacturing process development or characterization needs.

Lessons learned and challenges

Figure 3. Comparison of sample development timelines for traditional vs COVID-19 vaccines



* Vaccine development times vary widely, based on myriad factors.

Source: McKinsey & Company, 2021.[42]

The COVID-19 pandemic illustrates that the traditional, often time-consuming, barriers to vaccine development and authorization can effectively and efficiently be addressed, resulting in significantly faster development timelines (see Figure 3). Indeed, CEPI has gone one step further and called for vaccines to be ready for initial approval and mass manufacturing within 100 days of identifying the next pandemic pathogen (see Box 1).[43] These lessons learned can contribute to better preparation for future pandemics as well as creating a more efficient approach toward vaccine research, development and regulatory processes for epidemic and endemic diseases.

Box 1. The 100 Days Mission

In February 2021, G7 leaders – under the UK presidency – backed CEPI's ambitious plan to cut the time to develop new vaccines against emerging pathogens to just 100 days. This bold aspiration is now technically possible thanks to the radical scientific breakthroughs that have been made in response to the COVID-19 pandemic. Broadly, the global community will need to commit to the following steps in order to make the 100 Days Mission a reality:

- Optimize and compress the keys steps in the vaccine development process, including pre-clinical and clinical testing.
- Construct a global library of vaccine candidates against the ~25 viral families known to infect people.
- Begin clinical trials of potential vaccines almost immediately upon discovery of a novel outbreak, and run in parallel with rapid regulatory reviews to assess the benefits of a vaccine balanced against risk of infection and death.
- Regionally distribute manufacturing capabilities to enable rapid scale-up and delivery of vaccines.

If COVID-19 vaccines had been developed in 100 days, it would have saved millions of lives and trillions of dollars. Achieving the 100-day goal will give the world a fighting chance of containing future outbreaks before they spread globally and reach pandemic proportions.

Consistent and continued research funding is essential

COVID-19 vaccine development benefited greatly from decades of scientific R&D. Structural biology research into antigen design as well as vaccine platform development and identification of immune correlates of protection should continue to be funded.

Regulatory forums promote consensus among key regulatory authorities, reducing uncertainty for vaccine development timelines

The role of regulatory forums is critical to encourage open discussion between regulators and key stakeholders such as vaccine developers, vaccine manufacturers and country policymakers. Such forums can also

develop and release guidance documents to build trust and regulatory harmonization. However, this may not be fully replicable in a non-pandemic situation where the sense of urgency and societal impact may be lacking.

Disease variants will require new and flexible vaccine development solutions

Importantly, the recent surge of the Omicron variant of concern, with its multiple sub-variants with immune escape capabilities, bitterly reminds us that the COVID-19 pandemic has not gone away and that the development of new improved and more broadly protective vaccines is urgently needed.[44,45] Yet clinical testing for new vaccines is complex. The first COVID-19 vaccines were tested for efficacy in stringent placebo-controlled studies in individuals who were not SARS-CoV-2-infected.[46] The landscape has since dramatically and rapidly changed, as most of the population has now become SARS-CoV-2 seropositive due to vaccination (more than 60 percent),[47] infection, or both (hybrid immunity). Therefore, newly developed vaccines would need to be tested in SARS-CoV-2 seropositive individuals as a booster vaccine and assessed by immune responses against the variants of concern. Vaccines designed to induce mucosal immune responses may be more effective in reducing virus transmission but will require further efficacy trials. Developers and regulators are engaged in in-depth discussions for new clinical trial designs and vaccine approvals.

Government investment is critical to encourage future vaccine innovation and access

Sustained progress against the pandemic will require: development of new products that are effective against new variants; maintenance of the manufacturing capacity needed to quickly produce both existing and new products at scale; and measures to guarantee that these products remain broadly accessible and affordable. There is a strong economic case for continued national government investment in COVID-19 vaccines and therapeutics to encourage the private sector to continue to focus on this area and provide affordable and equitable access to these products. Direct government investment (or pooled multilateral investment in the case of CEPI) in the development, manufacturing and procurement of vaccines and therapeutics – and in ensuring affordable access to these products – has been key to overcoming these challenges to date and will remain important in the future.[48]

SECTION 2. ACCESS, EQUITY AND JUSTICE: COVID-19 VACCINES AND VACCINATION

Lois Privor-Dumm, Jean-Louis Excler, Sarah Gilbert, Salim Abdool Karim, Peter J Hotez, Didi Thompson, Soumya Swaminathan, Jerome H. Kim

To protect the world from the health, economic and social impacts of COVID-19 and future variants, every person must have access to vaccination. Yet, early in the pandemic, calls for global solidarity in ensuring equitable vaccine access were not heeded.[49] Recently, COVAX has made significant progress in accelerating the availability of vaccines.[50]

More than 11.5 billion doses of vaccines have been delivered since the end of April 2022[51] yet the goal of ensuring 70 percent vaccination coverage in each country has fallen woefully short in many parts of the world. As of mid-April 2022, 65 percent of the global population received at least one dose of a COVID-19 vaccine, but only 15 percent of people in low- and middle-income countries (LMICs),[52] below even the initial 20 percent population target to vaccinate health workers and those at highest risk,[53] and well below the current target of 70 percent.[54] As resources in countries continue to be diverted to fight the pandemic, particularly in unvaccinated or under-vaccinated populations, the concern is that the health, economic and social impact of COVID-19 may continue to rise and affect every part of the globe if we do not adjust our approach to the pandemic.

Ensure access, equity and justice – for vaccines and vaccination

WHO and other United Nations (UN) organizations define health equity in this context as: "vaccines…allocated across countries based on needs and regardless of economic status". This definition focuses on access, ensuring that poor countries have an equal ability to vaccinate their populations as rich countries. COVAX was set up with the principle of fair and equitable access at the core of its mission, and it aims to ensure rapid development, production and distribution of vaccines to all corners of the world to help end the crisis.[55] To achieve health equity, the conditions that can impact the ability to be healthy, for example, social determinants of health, are also needed.[56] The impact of the pandemic is exacerbated by conditions such as food and housing insecurity, environments leading to crowding, poor air quality, discrimination due to race, ethnicity and gender, lack of jobs and education, as well as access to healthcare, that have persisted in

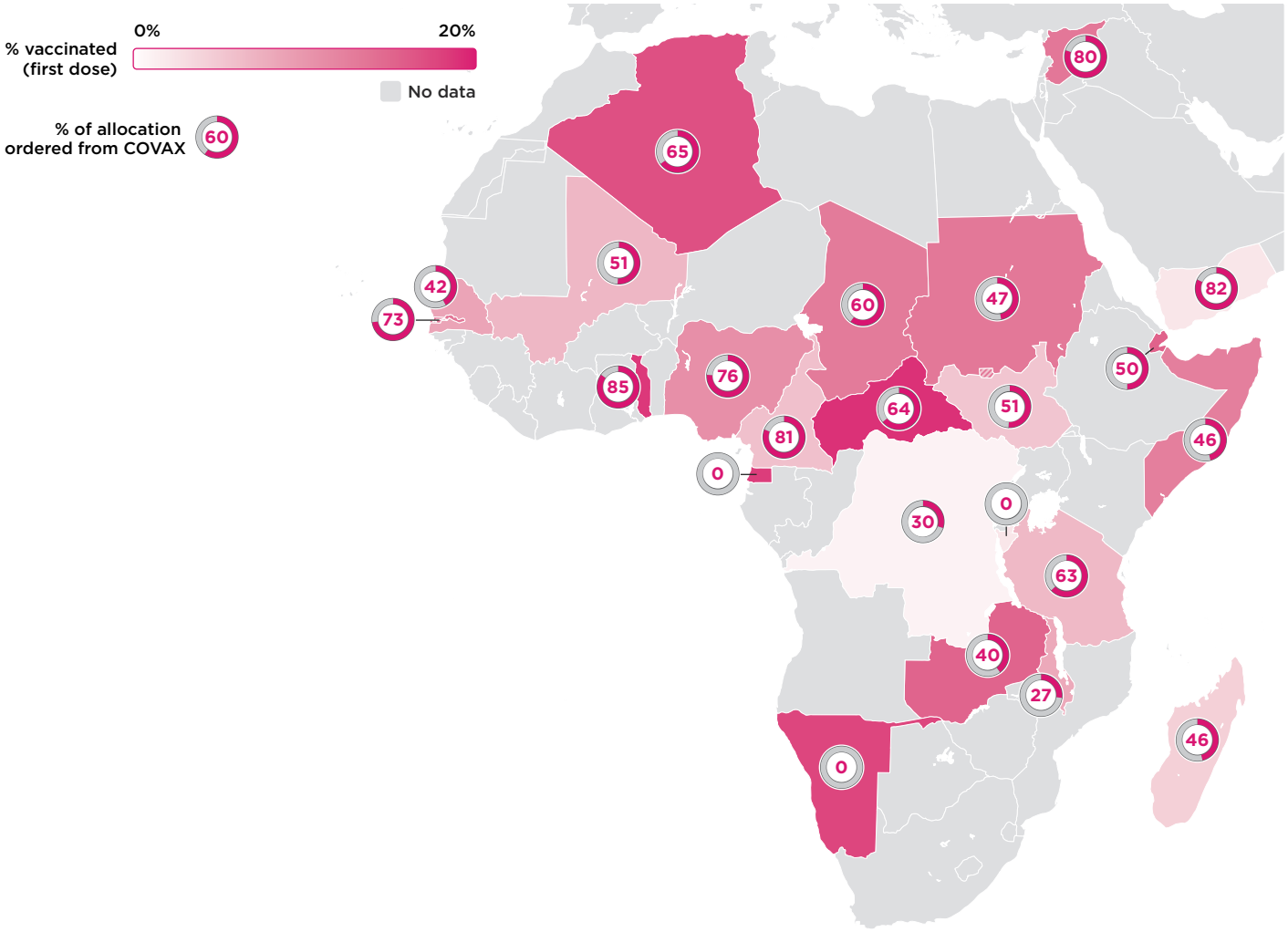
all countries, but particularly in LMICs, for a very long time. Removing or reducing the barriers to good health are at the core of achieving health justice and equity.[57,58] Some have called for ending "vaccine apartheid" to achieve justice, emphasizing it not as an act of charity, rather a need to address barriers to self-reliance and provide reparative justice.[59,60] Others, including those directly involved in COVAX, concur with the need to ensure that all countries receive their first dose before others receive the third or fourth. They do not go as far as wanting to tear down all existing structures, instead advocating for continuing improvements to ensure equity. This includes an emphasis on other pressing issues such as vaccination, including the increasing number of children who do not receive a single dose of any vaccine.[61] Yet, regardless of definition, we have not yet realized vaccine access, equity or justice.

Address sustainable and predictable demand to support continued supply for global vaccine equity

A number of factors have led to the inequitable distribution of and access to vaccines. To date, much of the debate has centered on a lack of supply and inequitable distribution due to vaccine nationalism, lack of vaccine manufacturing in LMICs, protection of vaccine intellectual property, a lack of affordability and transparency around pricing.[62,63] While all of these discussions have been happening, the need to directly engage with LMICs around demand has become more and more evident. As witnessed in previous pandemics, there is a danger of demand waning just as supply becomes available and the frustrations of not getting the product they wanted (mRNA) may also lead to further distrust or hesitancy.[64]

The outlook doesn't look good: despite availability of sufficient supply, countries with the lowest vaccination rates still have not ordered their allocation of vaccine (see Figure 4). Unpredictable or waning demand will most certainly have an impact on the ability to keep manufacturing plants producing. A lack of demand in the regions where supply has been problematic does not bode well for the future of regional manufacturing. One manufacturing facility in Africa may already need to close their doors due to a lack of demand.[65] Some countries may feel that, since they are not seeing big surges of disease, they are past the worst phase of the pandemic and can take other measures to control the pandemic or simply wait for a better vaccine. Yet we cannot risk countries or the global community moving on to other priorities, particularly as the risk of new variants has not passed.[66] We need open and honest dialogue about the expectations for the way forward to ensure that we don't face another

Figure 4. Low COVID-19 coverage countries: Doses allocated, ordered and received through COVAX



Country	Total number of COVAX doses allocated	Total number of COVAX doses ordered
Algeria	23,469,000	15,296,000
Burundi	0	0
Cameroon	1,871,000	1,521,000
Central African Republic	3,559,000	2,288,000
Chad	7,146,000	4,275,000
Democratic Republic of the Congo	17,409,000	5,150,000
Djibouti	537,000	271,000
Equatorial Guinea	0	0
The Gambia	885,000	649,000
Madagascar	6,806,000	3,156,000
Malawi	15,270,000	4,102,000

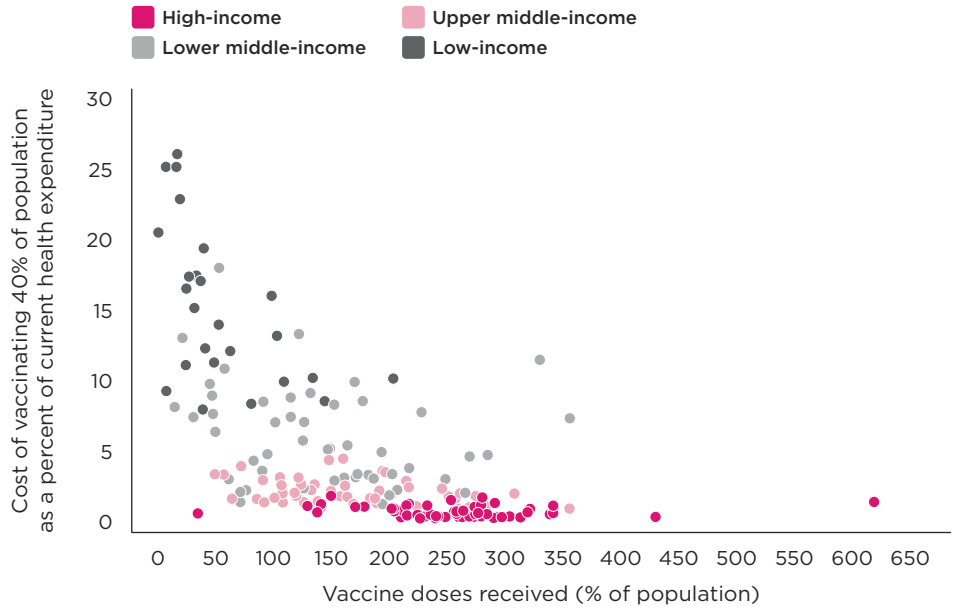
Country	Total number of COVAX doses allocated	Total number of COVAX doses ordered
Mali	7,092,000	3,613,000
Namibia	0	0
Nigeria	97,636,000	74,569,000
Senegal	10,619,000	4,474,000
Somalia	11,948,000	5,497,000
South Sudan	4,104,000	2,101,000
Sudan	20,518,000	9,741,000
Syria	14,294,000	11,446,000
Tanzania	12,360,000	7,750,000
Togo	4,415,000	3,747,000
Yemen	3,080,000	2,516,000
Zambia	16,718,000	6,650,000

Sources: Our World in Data; UNICEF Supply Division COVID-19 Vaccine Market Dashboard.

scenario where manufacturers, some of whom have received only minimal support from their government, finally have the vaccines, but no takers or no orders when expected, which furthers the risk of short-dated vaccines.

In Africa, the biggest concern now is not access to vaccines – this has not been restricted by supply since the first quarter of 2022 – but that access to vaccines is not convenient to citizens.[67] African leaders have outlined a variety of solutions to improve accountability, information sharing, engagement, and to address access obstacles in a more human-centered way. Some actions leverage existing platforms such as the US President's Emergency Plan for AIDS Relief (PEPFAR) and Malaria Initiative (PMI) or the Global Fund. Yet, while continuing the commitment to supply, perceptions about both the disease and vaccines also need to be addressed.[68] Vaccine misinformation and disinformation – especially on uncurated social media platforms – have had a substantial impact on vaccine uptake, in Africa as elsewhere.

Figure 5. Correlation between costs to vaccinate and doses received by income group



Source: UNDP Equity Dashboard.[69]

Some of the countries with the lowest vaccination rates, including the Democratic Republic of the Congo (DRC), Madagascar and South Sudan, estimate the cost of vaccinating 40 percent of their population at nearly 25 percent of their total health expenditure (Figure 5), and a UNDP/WHO/UNICEF survey reports an over 56 percent increase in expenditures needed to meet the 70 percent vaccination goal.[70] Many of the same countries have relatively low reported case counts and deaths, contributing to a perception of fewer cases of the disease.[71] It is not necessarily

for lack of planning – for example, in DRC, there have been efforts to engage the community, combat misinformation, and keep vaccination centers open, but the challenges of other diseases such as Ebola and malaria, an insufficient health system, and health workers who are overworked and underpaid, as well as other systemic issues of violence and mistrust in government have all contributed to limit progress.[72]

Health system capacity and acceptance of vaccinations are also important factors influencing vaccine uptake. More attention is needed to ensure that subnational variations are addressed.[73,74] Additionally, specific populations – including older adults, migrants, refugees and others – necessitate different delivery strategies. Few countries, for example, have vaccination programs for older adults, who may be less willing to attend vaccination centers or have other specific concerns that lead to vaccine hesitancy. Addressing the needs of this population requires advance planning and engagement with a coalition of partners who also have an interest in healthy aging and understand the unique concerns of this community. A more organized global effort, including a wide variety of country stakeholders who can identify relevant platforms and help build political will is needed, as well as partners on the ground to complement the activities of WHO and UNICEF, whose focus is largely on the younger age group.[75]

Ensure equity and promote trust at global and national levels

Research has shown that a globally co-ordinated approach is required to achieve speed of response and to bring the pandemic to an end.[76] But as supply issues ease, the equity progress among and within countries has stalled. Three actions are needed to ensure equitable allocations: products must fits countries' needs; financing must guarantee access; and sufficient demand must exist.[77] The first two areas have only been partially addressed. Vaccines were quickly developed and produced, including mRNA vaccines and vector-based vaccines; if all had gone according to plan, these would have provided 2 billion doses to vaccinate 20 percent of the population by the end of 2021. Although COVAX warned countries, there was little the organization could do to prevent limited supply and hoarding in the acute phase of the pandemic.[78] As a result, some countries felt the need to resort to bilateral deals at an elevated price.[79] The third area – sufficient demand – is perhaps the trickiest, as it is affected by, and impacts on the trust between all parties. In times of scarce supply, there needs to be demand from all countries and a way to monitor and enforce commitments when demand materializes. When Pfizer was asked about demand, they claimed they reached out to countries.[80] Whether they did or not, the perceptions have a way of creating distrust.

Govern towards health justice

Many countries have been unable to benefit fully from the advances in R&D, highlighting the urgency of revamping the R&D system and its governance.[81] Global models of governance are inherently complicated, and many parties want a seat at the table. There are many disparate interests that can be challenging to manage, but the responsibility of the co-ordinator is to bring multiple actors together to define collective action (such as solidarity) that benefits everyone.[82] In the case of COVAX, the equity goal was clearly defined, yet ignored. High- and middle-income countries undermined the COVAX model through bilateral deals; ironically, India, an LMIC itself, contributed to the problem by halting planned exports to take care of domestic concerns after a second wave of COVID.[83] Some perceive that a select number of global stakeholders – particularly donors and governments – moved forward with their own vision and vested interests rather than co-designing solutions that may have facilitated a better path forward.[84] At a country level, similar concerns of justice apply, as does the importance of accountability to ensure that access, equity and justice are achieved.

It is essential to have a shared vision of equity and a longer-term plan to ensure access to vaccines and supply security – not just for COVID-19, but other priority diseases. Countries may work with independent non-governmental organizations (NGOs) or a consortium of partners at regional level to provide support – for example, an Accelerated Development and Introduction Plan (ADIP) style or product development partnership. Africa has already taken measures to establish mRNA technology transfer hubs, and a new global biomanufacturing training hub in South Korea will assist in training a skilled workforce and strengthening regulatory capacity in these regions.[85] Hubs such as those in Africa and Asia may also offer opportunities to engage more closely with countries in these regions to build capacity, and to help integrate the demand-side intelligence that is needed to ensure that the needs of populations are taken into account and factored into accurate forecasts.

It is also important to acknowledge that measures of justice and equity are not solely about access to vaccines, but around vaccination. Systems to distribute routine immunizations may already be suboptimal in some countries; and vaccines for COVID-19 need to reach populations that aren't typically vaccinated. Additional support is needed to ensure that vaccines reach people. For instance, current COVID-19 vaccines require cold storage space at every level (including ultra-cold storage if they use any of the mRNA vaccines); the ability to manage cold-chain logistics and distribution is critical. Further, vaccine hesitancy and inability to access vaccines due to geographic and logistical hurdles pose challenges

in many LMICs. Regional and global actors play a role in supporting countries with limited health system strength, political will or resources to achieve targets set out by the global community.

Although vaccines were developed quickly to be distributed globally, that does not diminish the need for vaccines that work with existing platforms and particular countries' priorities. In future, vaccines that do not require refrigerated storage and can be administered as a pill, patch or nasal spray could obviate the need for highly trained healthcare workers to administer, and improve vaccine uptake. However, this will require investment in developing novel formulations followed by further clinical trials to assess safety, immunogenicity and efficacy. It will also likely require incentives, perhaps in the form of pull funding (funding for products shown to be effective) to ensure there is a market once products are developed. As we move past the acute phase of the pandemic, CEPI and other key funders should turn their focus to vaccines that address the specific needs of LMICs.

We can deliver services in the midst of existing inequity in poor countries – we have done it for AIDS with global solidarity (through the Global Fund to Fight AIDS, Tuberculosis and Malaria, and PEPFAR) and with political will at country level.[86] Strengthened engagement and co-ordination with existing priority programs can help intensify political will and lead to greater equity and justice through ownership of shared goals. A further outline of issues is provided in Figure 6.

Figure 6. Key issues of vaccine equity and justice

Issue	Description and impact	Potential solutions
 **Vaccine nationalism**	Hoarding of doses by high-income countries (HICs) leaves non-manufacturing low- and middle-income countries (LMICs) without coverage. Risk of variants, no end to pandemic.	Build on existing platforms such as President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to gain commitment in HICs, build capacity and provide needed services in addition to product.
 **Donations**	While doses are needed, supply is unpredictable and charity doesn't solve justice issues. Countries can't absorb short-dated product.	Donations directly to COVAX with adequate dating and the essential ancillaries to meet short-term needs while working for long-term solutions through regional manufacturing hubs.
 **Intellectual property**	This is highly complex as waiving of IP rights without technology transfer would result in the creation of multiple vaccines each requiring a separate path to licensure.	More balanced approach to limiting corporate profits on public goods while still incentivizing innovation.
 **Local manufacturing**	Enabling technology transfer to decentralize manufacturing and protect against scarcity with well-trained hubs. Fears have been around quality and training. Further, country-level intelligence is required to ensure that needs are being reflected in supply plans and product development.	Further develop the hub model in stepwise fashion to demonstrate ability not only with COVID-19, but other vaccines. Include understanding of country demand and needs in training to ensure that supply and demand are integrated. Ensure sufficient funding for sustainability of operations (see Section 1).
 **Affordability**	Vaccine hoarding can lead to high prices. Singular focus on pandemic may be unaffordable for countries and result in diversion of resources that exacerbates existing priority health issues.	Greater emphasis on health systems and sustainability of resources developed during the pandemic. Economic modeling to support donor funding of pandemic and other health issues.

Issue	Description and impact	Potential solutions
 **Lack of demand and trust**	Demand can be impacted by several things, including concerns about the vaccine itself (e.g., safety), the ability of the system to deliver vaccines, accessibility – particularly if deliberate efforts are not made to reach all populations – mistrust in the system at a global, national and local level. The perceived fairness of allocations also influences demand.	Enable more robust and authentic engagement through ensuring a meaningful voice at all levels. This may mean others outside of institutions leading debates and co-creation of shared strategies using a human-centered approach that addresses health systems' ability to equitably deliver vaccines to all populations. Growing anti-vaccine sentiment should be addressed in a deliberate manner (see Section 3). Accountability mechanisms must be present to ensure that strategies are implemented fairly. This would include public dashboards with disaggregated data to reach all populations. Use of trusted messengers, including faith and community leaders, and strategies to empower and engage communities. This is a complex issue that must be prioritized, perhaps through the use of nimble and honest brokers that interact with a variety of actors at global and regional levels (e.g., Gavi's Accelerated Development and Introduction Plans (ADIPs) or initiatives such as Malaria Vaccine Initiative, Haemophilus Influenzae type b (Hib) Initiative, and so on).
 **Inability to deliver doses sub-nationally or to specific populations**	Inequities exist at all levels, but the emphasis is often between countries rather than within a country. Underlying issues may range from a lack of political will, weak health systems, to competing priorities – these issues perpetuate the risk of the health needs of potentially vulnerable populations being left unaddressed.	Stronger systems to enable accountability, including disaggregated data on vaccine coverage, and furthering health system support as a key component of vaccine delivery. Ability to use pandemic funding for priorities that support existing systems and challenges exacerbated by the pandemic.

SECTION 3. COVID-19 VACCINES AND THE PANDEMIC: LESSONS LEARNED FOR OTHER NEGLECTED DISEASES AND FUTURE THREATS

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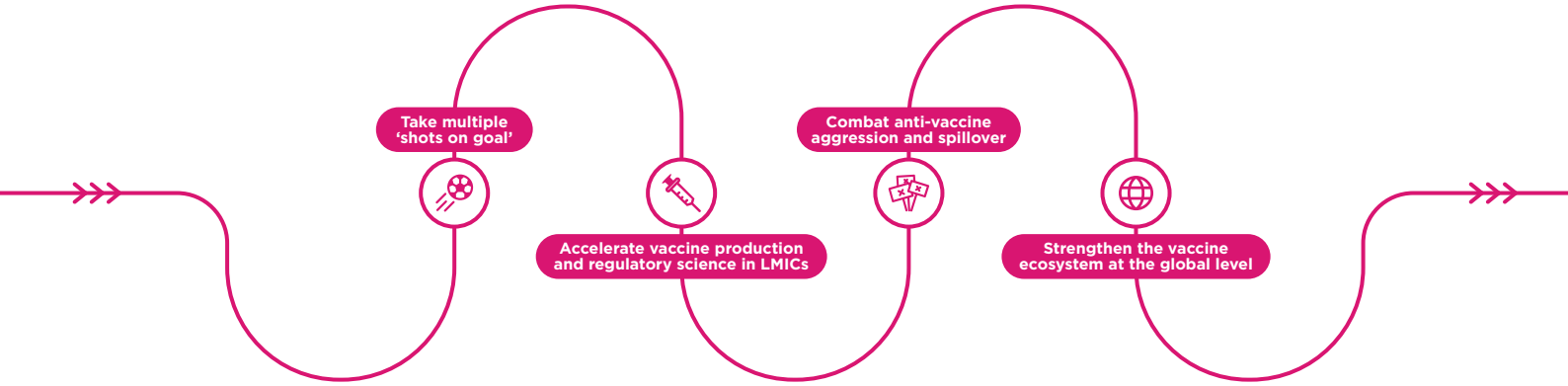
Figure 7. Lessons learned for other neglected diseases and future threats



The COVID-19 pandemic dramatically altered how scientific communities think about vaccine development, manufacturing, clinical testing – and ultimately emergency use release, licensure and global distribution. The COVID-19 vaccines that were licensed and delivered further affected public perceptions about scientific and medical research and the timelines required to have access to life-saving interventions. At the same time, vaccine supply tended to benefit wealthy nations at the expense of LMICs. Here we summarize the positive and negative aspects of the COVID-19 vaccine ecosystem, and how we might consider this experience as relevant for future vaccines for pandemic threats and global health inequities (summarized in Figure 7).

Take multiple 'shots on goal'

The COVID-19 pandemic emerged soon after a lesser-known public health triumph following the emergence of the Ebola pandemic in West Africa in 2014–2015.[87] Through the support of funds from the US Government under Obama's presidency, together with the Group of Seven (G7) inter-governmental forum, several promising Ebola vaccines were developed. They included a replication competent vesicular stomatitis virus

vaccine (VSV-EBOV), together with replication-defective adenovirus-5 (Ad5), Ad26, and chimpanzee (ChAd3) adenovirus-vectored vaccines, Modified Vaccinia Ankara (MVA) vaccines, and DNA vaccines, each proposed as a stand-alone technology or combined in prime-boost approaches.[88] VSV-EBOV advanced to efficacy trials, and vaccine effectiveness exceeded 90 percent.[89] An Ad26/MVA combination from Johnson & Johnson and from Bavarian Nordic[90] also attained WHO prequalification status. Ultimately, the Ebola vaccination strategy in the affected regions of the Democratic Republic of the Congo in 2019 helped to confine the spread of this highly lethal disease and possibly prevented a widespread epidemic regionally.

One lesson from the Ebola outbreak was the importance of having available multiple vaccine technologies tested against a single disease target in the expectation that at least one might advance in terms of proven efficacy, scale-up and delivery. A similar philosophy was used for the COVID-19 vaccine program in the US known as Operation Warp Speed,[91] and also with a broad portfolio of CEPI candidates, many national governments, and the ACT Accelerator and its COVAX vaccine-sharing facility. Through these initiatives, pharmaceutical companies in the US and Europe gained substantial financial and regulatory incentives to test and produce multiple vaccine candidates using innovative and novel mRNA, VSV, adenovirus, DNA and protein platforms.[92–95] Together the UK Government, CEPI, COVAX, or other organizations helped to support overlapping and unique vaccine technologies, including the AstraZeneca-Oxford adenovirus-vectored vaccine.

From these activities, multiple COVID-19 vaccines were developed, tested, approved and manufactured, saving millions of lives.[96]

From the Ebola epidemic of 2019 to the COVID-19 pandemic, a proof-of-concept portfolio approach testing multiple vaccine technologies has succeeded in slowing these diseases. It is not possible to predict which particular vaccine technology might prove to be successful (notably Merck's VSV platform, which succeeded in Ebola, was unsuccessful for COVID-19), but shaping a vaccine ecosystem in which multiple approaches are attempted in parallel should remain a priority for future pandemic threats.

This approach must also be used for new vaccines to combat long-standing infections for global health, including HIV/AIDS, tuberculosis, malaria, and poverty-related neglected tropical diseases. The acceleration and scaled-up production of new technologies for COVID-19 might help to facilitate vaccines for these more complicated targets.

Therefore, the innovations leading to mRNA, adenovirus, and protein subunit vaccines, and the ability to produce them at scale, might eventually apply to global health vaccines more broadly. Critical to the future success of this endeavor will be the ability to engage affected communities and ensure a reliable cold or freezer chain and delivery mechanisms to enable local health systems to provide vaccines and medications.

Accelerate vaccine production and regulatory science in low- and middle-income countries

The successes in vaccine development tell an incomplete story. More than 18 months after COVID-19 vaccines were first released, overwhelmingly they were secured for HICs in the northern hemisphere. Tragically, over this time, vaccine inequalities accelerated across LMICs in Africa, Southeast Asia, Central and South America, and the Caribbean (for example, Haiti and Jamaica). Almost 80 percent of the population of the US and Canada has received at least a single dose of COVID-19 vaccine, compared to only 20 percent in African countries.[97] The reasons for such global vaccine inequalities (explored in Section 2) include the agreements between G7 nations and multinational pharmaceutical companies for large volumes of new technology mRNA vaccine doses, and and the lack of funds available for COVAX to make early advance purchase agreements. As a result, Moderna and Pfizer-BioNTech initially sold most of their doses to HICs. Therefore, while there is no question that the mRNA lipid nanoparticle approach is an exciting one, the majority of doses were prioritized initially for high-income and upper-middle-income countries.

Where vaccines use new technologies, it is important to innovate to make them available to LMICs, while simultaneously making the appropriate funding and vaccine technologies available to producers in those countries. Most producers belong to a Developing Country Vaccine Manufacturers Network (DCVMN). The term 'appropriate' in this instance refers to the reality that the ability to make vaccine at a scale suitable for large populations is already in place.[98] For example, a large number of countries – including Argentina, Brazil, Cuba, Bangladesh, India, Indonesia, Thailand, China, and Vietnam – produce their own recombinant hepatitis B vaccine through microbial fermentation in yeast. Therefore, it would have made sense to provide global or large-scale financial support to vaccine producers in these countries to mass-produce a COVID-19 vaccine using both new and traditional approaches. Regarding the latter, this did eventually happen through a partnership between the Texas Children's Hospital Center for Vaccine Development and several developing country vaccine manufacturers. In India, this led to the production of

Corbevax, which was released for emergency use authorization in adults and children,[99] with almost 60 million doses administered so far. In the future, global R&D funders should make efforts to engage the major producers of global health vaccines to de-risk vaccine development efforts under the same terms as vaccine developers in HICs.

A parallel approach that also demonstrated some levels of success was to work to accelerate the transfer of new technologies for DCVMN members. For instance, together the UK Government, CEPI, and later COVAX supported the AstraZeneca vaccine, which early on made commitments to technology transfer for LMIC vaccine producers in Brazil, India and Thailand, while also supporting additional upstream technologies from Australia, China, South Korea and the US.[100] In addition, strong efforts were made to embrace Indian and South Korean manufacturers to produce the Novavax and the Johnson & Johnson vaccines,[101,102] while similar arrangements were made between Johnson & Johnson and Aspen Pharmacare in South Africa.[103]

Beyond these examples, technology transfer of mRNA and other approaches to LMIC or DCVMN vaccine producers will further strengthen manufacturing capacity. In the second year of the pandemic, WHO made a commitment to facilitate mRNA technology transfer to six countries in Africa – Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia – while the US-based Moderna made a commitment to build manufacturing capacity in Kenya.[104] A new Partnerships for African Vaccine Manufacturing group, in collaboration with the Africa Centers for Disease Control and Prevention and the African Union, has developed a framework for regional production of most of Africa's vaccines by 2040.[105] In parallel, the South Korean government and WHO have partnered with the International Vaccine Institute to train workers from LMICs in biomanufacturing.[106]

A key aspirational goal is the urgency to continue empowering DCVMN and LMIC vaccine producers, rather than the current model that relies predominantly on multinational companies. The approaches to consider include the possibility of further decentralization of global fund or donor initiatives to the Global South, including India and Africa. This approach embraces accelerating new and sustainable regional manufacturing hubs linked to LMIC and DCVMN vaccine producers. Making this commitment over an urgent timeframe might help to reshape the current model to more fully address global vaccine inequalities, while also highlighting the potential contributions of LMICs to vaccine innovation in the true spirit of vaccine diplomacy.[107,108]

A program of regulatory science capacity-building and strengthening is needed. This might include building capacity for LMIC regulatory authorities to become listed as 'stringent' by WHO. It could also include bringing others to maturity level 3 (ML-3) regulatory status. This will improve vaccine safety and the quality of regulatory review/advice in LMICs and will allow vaccines approved by that national regulatory authority to be considered by WHO for emergency use listing or prequalification. Such regulatory strengthening will further benefit vaccines developed for neglected diseases, because multinational vaccine manufacturers are not incentivized to make low-cost vaccines for problems found predominantly in LMICs.

Combat anti-vaccine sentiment

Another consideration is the realization that the anti-vaccine movement in its modern form, which began in England more than 20 years ago before it accelerated in the US, is now a global enterprise.[109] Anti-vaccine propaganda and disinformation is widespread across the African continent and LMICs in Asia, and there is an urgency to identify new means to counteract it.[110] Although anti-vaccine activities accelerated in the COVID-19 pandemic, they threaten critical progress made in childhood vaccination through the work of Gavi, the Vaccine Alliance, UNICEF and WHO.

The parallel threat is the more general erosion of trust and urgency in vaccinating the world's children. Creating a task force or committee that spans across the different UN agencies would acknowledge how the anti-vaccine movement has globalized, and also its complexity that reaches beyond the traditional health sector. In the US, anti-vaccine sentiment is now a major killer of young and middle-aged adults who refused COVID-19 vaccines, even after they became widely available.[111] We must recognize that the forces that caused so many Americans to shun vaccines have now expanded into Canada, Australia, Western Europe, Africa and Asia, resulting in unnecessary, vaccine-preventable deaths.[112]

Strengthen the vaccine ecosystem at the global level

The COVID-19 pandemic has revealed the geopolitical complexities of vaccine research, development, production, manufacture and distribution. Therefore, we should not rely on the health sector alone to correct past deficiencies. More than 18 million people have perished in the COVID-19 pandemic.[113] Averting future losses in human life from pandemics means we must consider responses systematically – including diagnostics,

therapeutics, vaccines, and personal protective equipment – and give pandemics the same status as other imminent threats, including global conflicts, cyberattacks, and other forms of terrorism. The Group of Twenty (G20) countries and their DCVMN and LMIC partners must take the lead and address the lessons learned, creating a more robust, co-ordinated, and effective pandemic response.

We must also rely on civil society and community-level efforts. Otherwise, we risk repeating the failures of the past. Moving forward, we must consider a new level of financial investment, co-ordinated by the G20, but potentially from multiple funding sources, and with input and advice from CEPI and the Biomedical Advanced Research and Development Authority. At the 2021 G20 Summit in Rome, the G20 Leaders' Declaration specifically emphasized some of these elements, including mRNA hubs for COVID-19 vaccines in South Africa, Brazil and Argentina, with a goal to broaden the list of COVID-19 vaccines authorized for emergency use listing.[114]

These activities must now be generalized to include vaccines for major global health infections that include neglected diseases and potential pandemic threats. To be successful and sustainable, these manufacturing initiatives must be accompanied by meaningful strengthening of systems to create a robust vaccine ecosystem. To realize greater equity and access to vaccines in future pandemics, this must include improvements in regulatory capacity, vaccine research and development funding, and education and training of the biomanufacturing and research workforce in LMICs. Creating a robust distributed system for vaccine research, development and manufacturing will be long and difficult, but the lessons learned from the COVID-19 pandemic make this essential.

Summary recommendations

We offer the following summary recommendations for future consideration to combat global infections that cover neglected diseases – HIV/AIDS, malaria, tuberculosis, and neglected tropical diseases – and pandemic threats.

Take multiple 'shots on goal'

1. Continue the 'multiple shots on goal' approach to new vaccine, which embraces simultaneous technologies to include, when feasible, VSV, adenovirus, mRNA, whole inactivated virus, nanoparticle and recombinant protein technologies.

Accelerate vaccine production and regulatory science in low- and middle-income countries

2. Expand sustainable scale-up capacity for these technologies, potentially at individual or multiple hubs.

3. Encourage and support the development of indigenous and appropriate vaccine technologies already in place for DCVMN vaccine producers.

4. In parallel, support the transfer of new technologies to DCVMN producers.

5. Strengthen existing capacity for LMIC national regulatory authorities and expand the number of ML-3 level national regulatory authorities.

Combat anti-vaccine sentiment

6. Take a more strategic approach to combating anti-vaccine activism, especially now that the anti-vaccine movement permeates many LMICs.

Strengthen the vaccine ecosystem at the global level

7. Establish a G20 framework for DCVMN and LMIC partners to promote, support and (in some cases) harmonize a more robust, co-ordinated, and effective pandemic response.

8. Encourage and embrace feedback from civil society and community-level in-country organizations.

SECTION 4. CONCLUSION

The COVID-19 pandemic triggered a global sense of vulnerability and urgency that led to concerted action by governments, funders, regulators and industry to overcome traditional challenges for vaccine development and authorization. Several factors increased the speed of COVID-19 vaccine development, including past research investments, pandemic urgency, unprecedented financial investment, massive and sustained demand, expedited regulatory review, and accelerated clinical testing. The rapid research and development involved in COVID-19 vaccines has created a new era of vaccinology – powerful platform technologies and a transformed vaccine industry should benefit all populations, including the most vulnerable.

Governments and funders must learn from the lessons of the COVID-19 pandemic to build a more efficient and effective vaccine ecosystem that can protect populations from other pandemic, epidemic and endemic disease threats. Now is the time to take a longer-term view and ensure that investments are not just made in the early winners, but that, as new vaccines are developed, there are incentives to build expertise – in particular, in manufacturing that can be leveraged for LMICs and other markets to ensure equity in innovation, access and delivery.

It is equally critical to invest in the necessary infrastructure to improve capacity, know-how, efficiency, and success in the development of vaccines for other infectious diseases.

LMIC vaccine producers must be prioritized at the outset, along with multinational pharmaceutical companies. These LMIC vaccine producers must be encouraged to pursue vaccines based on their existing capabilities, but also afforded opportunities to receive new technologies along with support for rapid scale-up of production. The creation of vaccine manufacturing hubs, such as the Partnerships for African Vaccine Manufacturing, is certainly a future solution for a new public health order which will safeguard the health and economic security of the continent and guarantee vaccine security and access.

The G20 nations, especially the large middle-income countries, must assert greater ownership to support LMIC vaccine producers and national regulatory authorities through better organized and funded initiatives. Civil societies also have important and mission-critical roles to build a well-functioning vaccine ecosystem. In parallel, the G20 nations and civil societies must acknowledge the critical need to maintain or restore trust among their populations.

We must also not lose sight of vaccine access, equity and justice – for vaccine supply, but also for *vaccination* and the social determinants of health. There needs to be more sharing of vaccine manufacturing capabilities integrated with better intelligence about demand-side concerns to ensure sustainable access at a regional level. More planning, resources and program implementation capacity are needed on vaccination at a *country and community level* to ensure predictable demand to keep in balance with an increased supply. Even in settings of high vaccination coverage, vaccination rates may still be suboptimal in hard-to-reach and vulnerable groups. Systems and granular monitoring must be strengthened to make vaccination more accessible and acceptable across disparate groups.

Humility and perseverance are perhaps the two most important lessons learned from the pandemic. Despite differing views on vaccine equity and justice, the global health community must come together with governments, manufacturers and donors to co-create strategies that ensure access, equity and justice.

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