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Commentary
Global COVID-19 vaccine inequity: The scope, the impact, and the challenges

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Global vaccine inequity is prolonging the COVID-19 pandemic. Here, we outline the scope and impact of inequitable vaccine distribution and identify challenges in vaccine development, manufacturing, and distribution as well as potential solutions to address this crisis.

Introduction
Within a year of the initially reported cluster of COVID-19 in Wuhan City in China, the first preventative vaccinations against the novel coronavirus, SARS-CoV-2, were administered in the United Kingdom on December 8th, 2020, followed by the approval and administration of multiple other vaccine candidates globally (Leford, 2021). With funding and political commitment, the development and the manufacturing of vaccines could take advantage of existing science and be accelerated well beyond the typical process of 5 to 10 years. However, the discourse has increasingly shifted to the looming risk of inequitable global distribution of developed vaccines and whether the same urgency can be mounted to address it. At present, the scope of global COVID-19 vaccine inequity is immense, and its repercussions are and will continue to be felt worldwide. While initiatives such as COVAX have made some progress in mitigating inequitable vaccine distribution, these efforts currently appear insufficient to address the scale of global need. We outline the scope and impact of inequitable vaccine distribution and discuss major diplomatic initiatives, such as COVAX, targeted to address vaccine inequity. We will summarize the pitfalls to equity in the vaccine research and development pipeline, ranging from intellectual property to manufacturing and regulatory considerations. Finally, we will highlight bold new steps such as updating international agreements and capacity building that should be undertaken in the long term to address this global crisis and the next one.

The scope of global vaccine inequity
As the pandemic abates in many high-income countries (HICs), cases and mortality continue to increase in many LMICs (low- and middle-income countries) (The Economist, 2021a). At time of writing, almost 85% of global vaccine doses administered have been in high- and upper-middle-income countries and 75% of those have been administered in just 10 countries, including the United States, the United Kingdom, Germany, and France (Mathieu et al., 2021). Only 5% of the world has received one dose of the vaccine, and the inequalities are even more profound in areas such as the continent of Africa where most countries have administered doses to less than 1% of their population.

So far, these stark disparities appear to follow the same sequence of events that have been encountered during prior pandemics. During the 2009 H1N1 pandemic, developed countries initially purchased and stockpiled as much vaccine as was manufactured. Even when WHO and UN intervened to try and secure vaccines for developing countries, donations to LMICs were often limited (Eccleston-Turner and Upton, 2021).

The impact of global vaccine inequity
Inequities in vaccine coverage will and are resulting in both direct and indirect consequences, in affected countries and the overall global community. Aside from the direct illnesses and loss of life, continued vulnerability to surges in cases leaves already struggling healthcare systems with limited ability to provide care for other health conditions. Illness and deaths among healthcare workers impacts the human resources required for continued response to COVID-19 and non-COVID-19 health burdens. Over the last year, rates of childhood vaccination have dropped precipitously due to postponed vaccination campaigns, delaying immunization to 13.5 million people in some of the most vulnerable countries in the world (U.S. Global Leadership Coalition, 2021). Lastly, continued transmission of COVID-19 creates a scenario conducive to continued viral evolution and development of new mutations, some of which may confer selective advantage in terms of transmission or immune evasion as has already been occurring over the past year. These viral variants could pose a threat to individuals in HICs, particularly those who are unvaccinated or those who cannot mount a high enough immune response to vaccination. Additionally, overwhelmed healthcare and surveillance systems are also less likely to detect new emerging and endemic infectious diseases threats that may arise. In 2020, 1 million people were undiagnosed and untreated for tuberculosis, understarking over a decade of investment in curbing this disease globally.

Beyond direct health impacts, the ongoing diversion of resources to
COVID-19 response can keep countries from returning to normal socially and economically (U.S. Global Leadership Coalition, 2021). As communities around the world deal with the wreckage of their economies, 95 million more people have been pushed into extreme poverty, with another 200 million predicted to be at risk between now and the year 2030. The pandemic has also led to worsening food insecurity and has had detrimental effects on global childhood education and women’s empowerment. The longer the COVID-19 pandemic continues as an acute crisis in LMICs, the greater the likely devastation to all the above indicators.

However, the economic toll of unequal vaccine allocation is also going to impact the entire global market. A RAND Europe report estimates that if the poorest countries cannot access the vaccine, the world would still lose $153 billion a year in GDP (including a loss of $40 billion in EU and $16 billion in US) (Hafner et al., 2020). Given these economic costs, HICs would get back about $4.8 for every $1 spent on supplying vaccine.

The urgency for global vaccine coverage is even greater now in the face of more transmissible variants that seem to be causing a surge of cases in countries that were initially thought to have escaped the worst impact of the pandemic due in part to a younger population. Surges in Brazil and India appear to be fueling case increases in countries surrounding them due to variants that seem to affect younger patients more than the initial virus, and in some cases causing re-infections in those with prior immunity through natural infection. The case of India highlighted the possibility that large gatherings and multiple introductions of these variants could create an environment where more LMICs may see large surges, making the speed of vaccination paramount. New outbreaks across sections of Africa, Asia, Latin America, and Russia in July 2021 appear to confirm these fears.

**COVAX and vaccine diplomacy**

WHO’s COVAX utility represents the vaccine pillar of the multi-lateral, multi-organizational ACT-Accelerator and was formed in part to address the delay that was seen in access and distribution of H1N1 vaccines to LMICs (Eccleston-Turner and Upton, 2021). COVAX is a partnership between WHO, the Coalition for Epidemic Preparedness Innovations, the Global Alliance for Vaccines and Immunizations (Gavi), and UNICEF. Its ambitious goal is both to support research and development and to use financial commitment of purchase by rich countries to provide doses of successful vaccine candidates for 20% of the population in 92 of the poorest countries (Eccleston-Turner and Upton, 2021). Several barriers currently hinder its ability to meet its goal by the end of 2021. First, COVAX faces a funding gap of $3.7 billion dollars immediately (which the US has promised to help cover in the short term) and an additional $23.7 billion over the course of the next year. Second, COVAX has not been able to compete with HICs on the global market, which have already purchased a huge portion of the available supply of approved vaccines. Despite joining COVAX, many HICs established their own bilateral agreements with vaccine manufacturers. As discussed in detail below, further production of vaccines is currently plagued with shortage of raw materials and limits on manufacturing capacity. Third, COVAX faced another large challenge when one of its largest contracted producers, Serum Institute of India, fell behind on its targets and eventually delayed the anticipated date of export due to the large surge of COVID-19 cases during India’s second wave (Cohen and Kupferschmidt, 2021). As a result, COVAX will face a vaccine shortage, even as India itself recovers from a devastating public health emergency and tries to balance domestic needs with international commitments for manufacturing.

Moving forward, the speed of global vaccination is paramount in the advent of new highly transmissible variants as is responsiveness to geographic areas facing acute surges. Some have criticized the COVAX utility for not being responsive enough to new surges in LMICs, by continuing to distribute vaccines based on country’s population, rather than on severity of outbreaks or resilience of affected healthcare systems to handle such surges (Herzog et al., 2021).

Against this backdrop, a perverse juxtaposition is arising where many HICs are predicted to have a large surplus of vaccines, with the US predicted to have nearly 1 billion doses in surplus despite vaccinating everyone over 5 years of age and keeping stockpiles (Evenett, 2021). Although HICs have started to make both bilateral donations and further commitment of doses to COVAX, to date these donations to not approach the scale of what is needed. For example, G7 countries recently announced a pledge of 870 million vaccine doses to LMICs, whereas the WHO estimates that 11 billion will be needed to vaccinate 70% of the global population (Wise, 2021). Alternatively, China and Russia, who did not partake in COVAX, are providing doses of domestically developed vaccine candidates (such as Sputnik, Sinopharm, and Sinovac) through bilateral agreements, which they hope will improve their global standing, while improving relationships and providing strategic influence (The Economist, 2021b).

**Barriers to expanding vaccine manufacturing**

The advent of next-generation, “plug and play” vaccines utilizing mRNA, viral vector, or protein subunit technology offers opportunities to develop new products to reduce the burden of infectious diseases. During the COVID-19 pandemic, the use of these technologies demonstrated the speed at which a new vaccine could be developed. However, difficulties in scaling the production of these vaccines to achieve global vaccine equity highlights the challenges that these new technologies still face in meeting global demand. Legal barriers, including intellectual property transfer, are well known in the field of therapeutic technology development. But beyond familiar legal and regulatory hurdles, scaling next-generation vaccine production confronts barriers including a lack of physical infrastructure, technical expertise, and supply chain capability (Wouters et al., 2021).

Next-generation COVID-19 vaccines incorporate a large number of patent-protected technologies, ranging from the modified adenoviral vectors to the lipid
nanoparticles used to deliver mRNA and the design of a stabilized SARS-CoV-2 spike protein that serves as the critical antigen for multiple vaccines. Liberalizing intellectual property rules around these innovations via a Trade-Related Aspects of Intellectual Property Rights (TRIPS) waiver would make these underlying technologies available for use at a global scale. Proponents point to the Treatment Action Campaign and the TRIPS waiver granted for antiretroviral therapies as evidence that this approach can greatly improve access to COVID-19 vaccines. However, as many vaccine developers actively worked to set up licensing agreements or pledged not to enforce patent protections for COVID-19 vaccines, legal barriers may not be the primary barrier to global vaccine equity. In this event, liberalizing patent laws is a first step toward improving equity but will not be the whole solution.

Production and supply chain barriers remain a larger constraint on global vaccine equity. The ability to produce complex biologic products, including vaccines, remains highly unequal and concentrated in certain countries, including the United States, European Union, India, and China. Entire continents, such as Africa, broadly lack vaccine manufacturing capacity, despite having “finish and fill” capabilities. COVID-19 vaccines made in Africa currently utilize active ingredient produced abroad and shipped to these “finish and fill” facilities—at this time there are no complete COVID-19 manufacturing chains in Africa (Gennari, 2021). This is, in part, a side effect of a constricted supply chain that uses highly specialized materials. For example, the mRNA caps utilized in mRNA vaccine manufacture are primarily produced by a single company that holds the IP rights. Ionizable cationic lipids, which are critical for mRNA vaccine delivery, are subject to a considerable supply bottleneck—limiting the number of doses of mRNA vaccine that can be produced. Currently, the technical capabilities of the vaccine manufacturers that do exist in Africa to produce next-generation vaccines is likely limited.

Legal and production barriers to expanding vaccine production are further compounded by technical barriers related to technology transfer and regulatory capacity, such as the concentration of vaccine production knowledge in companies in HiCs and the current dearth of trained personnel in LMICs (Price et al., 2020; Wouters et al., 2021). The lack of research and development infrastructure and personnel in LMICs is a significant challenge to vaccine technology transfer and reflects overall urgency for international investment in research capacity strengthening for this and future threats. Likewise, the weaker regulatory and surveillance capacity in many LMICs represents a technical barrier to both producing high-quality vaccines that are safe and efficacious and monitoring the safety of vaccines as they are administered using domestic surveillance capabilities, as opposed to relying on WHO adverse event monitoring (Lurie et al., 2020). This is a critical barrier to where the manufacturing and deployment of in-country manufactured vaccines can be expanded: the WHO estimates that only 30% of national regulators have the current capability to effectively oversee vaccine manufacturing and administration of those vaccines. Together, these challenges represent immediate barriers to expansion manufacturing capacity but also highlight areas where global investment needs to focus moving forward.

**Overcoming barriers to vaccine equity**

The first step toward meeting the current global need must be redistribution of surplus that is starting to develop in some high-income countries. Alternatives, such as increasing production capacity where it is currently possible and then facilitating the export of vaccine components, including active ingredient, to finish and fill facilities globally would ensure that vaccines reach markets with critical need. Continuing research and development, including support through expensive clinical trials, of additional COVID-19 vaccine candidates would further serve to increase supply. Were these candidates (such as protein subunit vaccines) to use different components than mRNA or viral vector-based vaccines, they may not be subject to the same supply chain bottlenecks currently constraining vaccine production. Moreover, initiatives such as COVAX continue to require full funding in order to ensure that COVID-19 vaccine production continues even as demand for vaccines in upper-income countries wanes. Over the next year these actions could dramatically improve equitable access to vaccines.

The possible approval of TRIPS waiver for COVID-19 vaccine intellectual property signals a desire to strive for global vaccine equity but true global vaccine equity will require a long-term, global effort to expand vaccine production capability, facilitate technology transfer, and develop regulatory systems that support vaccine innovation. Efforts are underway, financed by development banks and international development agencies, to expand the physical infrastructure necessary for vaccine production where it is currently nonexistent. Facilitating technology transfer and improving regulatory capability receive less priority—a critical oversight given the importance of a supportive scientific ecosystem to facilitating vaccine development.

Facilitating technology transfer could be paired with efforts to support the transfer of intellectual property rights for vaccines and their underlying components. A system in which established vaccine developers provide production know how to new vaccine manufacturers while licensing their products to these manufacturers would allow them to generate revenue from the use of their technology, while boosting vaccine manufacturing capacity globally. These efforts could be paired with commitments from vaccination programs to purchase vaccines locally, where possible, to support local manufacturers. The African vaccine market, in 2020, was estimated to be worth $1.2 billion annually, with 99% of vaccines imported from outside the continent. There is a market for vaccines that could be transitioned to local production. Moreover, as vaccine candidates for malaria and other endemic diseases that use next-generation vaccine technologies are developed, the size of the market for locally produced, next-generation vaccines will continue to grow.

Improving biopharmaceutical regulatory capacity, on a global scale, could be achieved by increasing collaborative programs between regulatory agencies. As part of their global health initiatives, the Centers for Disease Control and Prevention (CDC) regularly engages peer institutions to boost surveillance and infectious disease management capabilities. This
model could be utilized by the Food and Drug Administration (or other medical regulatory agencies) to boost the regulatory capabilities of peer institutions beyond their current efforts. Such activities should include improving the regulatory capabilities identified as critical in the Global Health Security Index (GHSI) (which was developed to measure readiness of countries to combat infectious disease threats across different sectors), as well as improving capabilities related to vaccine production and post-market adverse event monitoring where appropriate. Regulation is critical to ensuring the safe manufacture, utilizing good manufacturing practices, and use of vaccines, both traditional and next generation. For vaccine production to move forward in new markets and meet WHO standards, it is critical for a robust regulatory apparatus to be in place. The ability to regulate the manufacture of medical countermeasures, such as vaccines, and monitor their use during deployment (to detect adverse events and reduce the burden on WHO personnel) should be made a component of GHSI scoring.

Conclusions

Dr. Tedros Adhanom Ghebreyesus, Director-General of the WHO, has called global vaccine equity “the challenge of our time.” Although achieving global COVID-19 vaccine coverage is clearly tied to all of our mutual return to normalcy and long-term recovery, it also poses an unprecedented need for global investment, coordination, and solidarity. It represents the first test of whether the global community has recognized the importance of escaping the cycle of panic and neglect that generally follows emerging infectious diseases threats.

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