



Reducing Global COVID Vaccine Shortages: New Research and Recommendations for US Leadership

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Disclosures

Mark McClellan, MD, PhD, directs the Duke-Margolis Center for Health Policy, was Commissioner of the Food and Drug Administration from 2002-04 and Administrator of the Centers for Medicare and Medicaid Services from 2004-06. He is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomiQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

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This Duke-Margolis resource on COVID-19 response policies is intended to inform and help guide policy makers addressing the evolving COVID-19 pandemic in the United States and around the globe, and will be updated as the pandemic and response capabilities change over time.

It contains recommendations for a U.S. Federal response as well as steps and resources for stakeholders across the health care ecosystem. We will add further resources to address a range of related, critical policy challenges.

We thank our many collaborators, co-authors, and reviewers who have contributed significant expertise and guidance on these rapidly evolving issues. Please reach out to us with additional suggestions for resources and effective policies at dukemargolis@duke.edu - we welcome your input.

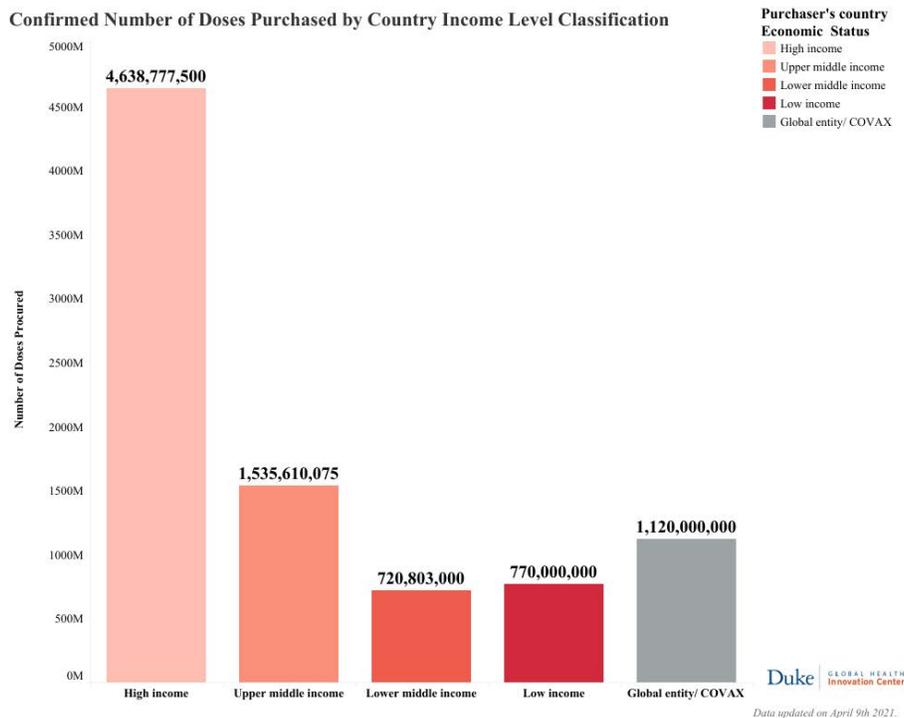
A small number of high- and middle-income nations and regions including the United States (US), United Kingdom (UK), the European Union (EU), China, and India account for the majority of COVID-19 vaccines administered thus far. The uneven global distribution of COVID-19 vaccines has raised concerns and spurred demand for action to ensure equitable access, including growing calls to waive intellectual property protections. There are a number of challenges to scaling-up global access beyond intellectual property barriers, and addressing these challenges requires a multipronged, coordinated approach. Leadership from the US on safe, effective, and equitable global access to COVID-19 vaccines is imperative.

In this paper, we present the scope of the global vaccine access challenge, and propose a complementary three-part US-led solution that: 1) increases and leverages funding for the global effort to advance vaccine access through COVAX; 2) undertakes coordinated bilateral and multilateral mechanisms to provide excess doses to countries in need; and 3) increases safe and reliable manufacturing and distribution capacity.

The Challenge of Global Vaccine Equity

Just four nations or regions with less than half the world's population have administered seventy percent of all COVID-19 vaccine doses, while the poorest countries have barely begun vaccinating due to lack of funding and supply. The world's wealthiest nations have locked up much of the near-term supply. Indeed, while [confirmed purchases](#) of vaccines globally cover 8.6 billion doses,

the world’s high-income countries, with a population of 1.2 billion (16% of global population), account for 4.6 billion doses (53% of all purchased doses), while low-income countries hold just 770 million doses. Finally, even if [COVAX](#), the global COVID-19 vaccine mechanism, were to be fully funded this year, it would still vaccinate only 20-25% of the population of the world’s 92 poorest countries. At the current rate, these countries may not reach 60% coverage until 2023 or later. Beyond access to vaccines, reaching high and equitable vaccination rates, especially in low-resource settings, will require significant investment and assistance in supply chain and logistics, training and availability of health workers, appropriate regulatory oversight, and efforts to combat vaccine misinformation and hesitancy.



Meanwhile, the virus will continue to circulate in these countries and new variants will emerge, threatening the US and the world and slowing global economic recovery. In short, the pandemic will not end anywhere until it ends everywhere. It is in the US interest to proactively and urgently address COVID-19 vaccine inequity. Furthermore, vocal US leadership on the global stage is imperative for a more effective and coordinated global response using rigorously monitored and highly effective vaccines, at a time when nations such as China and Russia are attempting to gain influence through vaccine diplomacy.

Waiving Intellectual Property Protections Won't Achieve Vaccine Equity

To address global access to COVID-19 vaccines and therapies under emergent circumstances, India, South Africa, and other nations [have moved](#) to temporarily waive World Trade Organization (WTO) provisions under the Agreement on Trade-Related Aspects of Intellectual

Property Rights (TRIPS) for the duration of the pandemic. The waiver would remove intellectual property protections for patents, industrial designs, trade secrets, and regulatory data for COVID-19 vaccines and therapies.

While genuine and well-intentioned [proponents](#) of this waiver [believe](#) it will remove a significant barrier to increasing production and access, major scale-up of safe and reliable vaccine manufacturing requires overcoming a range of other challenges. Without ensuring adequate supply of key ingredients (e.g., lipids, vials, bags for bioreactors, etc.), new efforts would likely complicate the fulfillment of existing contracts for authorized vaccines. High-quality vaccine manufacturing is complex, requiring extensive technical knowhow and high-quality regulatory oversight, and experienced manufacturers will not participate without a no-fault compensation scheme to protect vaccine users in case of a serious adverse event. The unintended result could be less effective pandemic control, either because of compromised effectiveness of such vaccines or compromised public confidence in vaccination, leading to greater outbreaks and more variants. Global vaccine supply must be scaled up rapidly, without compromising safety or quality.

WTO Director General Ngozi Okonjo-Iweala has proposed a [“third way”](#) alternative to a TRIPS waiver or direct vaccine supply. While not yet fully developed, this could include use of voluntary licensing arrangements to increase manufacturing capacity. Such arrangements would involve public-private partnerships that assure the transfer and use of the manufacturing quality knowhow needed for timely production of safe and effective vaccines. Similar models are already being implemented in India, Thailand, and elsewhere, through public-private partnerships with support from private philanthropy and investment of private capital.

US Leadership for a Three-Part Solution

To ensure global vaccine equity, a US-led Global Vaccine Access Initiative could build on prior US-led efforts, including the President’s Emergency Plan for AIDS Relief (PEPFAR), and the idea of a “third way” to address global shortages more quickly and efficiently. Other health policy leaders have recently proposed [solutions](#) consistent with this recommended approach.

I. Leverage US Funding to Enhance Impact of COVAX

COVAX is part of the [ACT-Accelerator \(ACT-A\)](#), which was launched in mid-2020 to support the global response to the COVID-19 pandemic by focusing on four pillars of work: vaccines, therapeutics, diagnostics, and health system strengthening. ACT-A’s proposed budget for 2020-21 is \$33.2 billion. However, overall [contributions](#) to ACT-A, as of early March 2021 are only \$11.2 billion, leaving an overall funding gap of \$22.1 billion. (First figure)

ACT Accelerator budget and funding gap by pillar

Pillar	ACT-A 2020-21 budget as of Sept 2020	Cost adjustments (1)	Contributions	2021 funding gap
Vaccines	16.0	-4.3	8.6	3.1
Therapeutics	6.6	-2.7	0.7	3.2
Diagnostics	6.0	+3.7	1.0	8.7
Health Systems Connector	9.5	-1.6	0.6	7.3
Sub-total	38.1	-4.9	10.8	22.3
ACT-A pending allocation (2)			0.2	-0.2
Total	38.1	-4.9	11.0	22.1

NOTE: all figures are rounded. Contributions to Pillars are subject to FX variation.

Source: <https://www.who.int/publications/m/item/access-to-covid-19-tools-tracker>

COVAX, co-led by the World Health Organization (WHO), Gavi, the Vaccine Alliance, and the Coalition for Epidemic Preparedness Innovations (CEPI), serves as the vaccines pillar of ACT-A. Its proposed 2020-21 budget is \$11.7 billion. Total contributions as of early April are \$8.6 billion, leaving a funding gap of \$3.1 billion. The US has [committed](#) a total of \$4 billion to Gavi to support COVAX, with [release](#) of \$2-2.5 billion to support vaccine procurement in 2021 for the COVAX advance market commitment (AMC) eligible participants. The most urgent financing need for COVAX is an [additional \\$2 billion](#) to purchase vaccine doses for delivery through the COVAX AMC in 2021, in order to meet its goal of providing vaccines for 20% population coverage for 92 eligible countries.

The US is leveraging its [current role](#) in the Investment Opportunity for Gavi COVAX Advance Market Commitments (AMC), with its promise to release its additional \$1-1.5 billion commitment based on additional pledges and fulfilment of pledges by other nations toward COVAX. The US could also leverage its participation in the upcoming UK-hosted G7 Summit to encourage a G7/G20 commitment to assist with the funding gap for COVAX as well as ACT-A more broadly.

In conjunction with additional funding, opportunities exist to increase the impact of COVAX activities as we describe below.

II. *Lead Development of Plan for Distributing Excess Vaccines*

High-income countries, especially in Europe, are facing demand that exceeds supply for vaccines right now, as well as serious ongoing outbreaks. But that will change in the coming weeks to months, as their advance purchase contracts are fulfilled. The situation is the same in India, which supplies vaccines to more than 70 countries.

The US government has entered into advance purchase agreements and provided financial support and/or assistance to rapidly scale the vaccine manufacturing capacity for vaccines produced by Pfizer/BioNTech, Moderna, Johnson & Johnson, AstraZeneca, and NovaVax. Recognizing that projections are dynamic and open to changes over time, we currently estimate that the US will likely have 300 million or more excess doses of vaccines authorized in the US and/or EU by the end of July, based on existing authorizations and purchase agreements, and assuming the emergency use authorization of the Novavax vaccine. This estimate accounts for the US retaining enough vaccine supply to vaccinate the vast majority of children. With US support, manufacturing capacity across the five manufacturers that have advance purchase agreements is continuing to ramp up, with nearly 200 million doses per month expected in June and July and over 300 million per month by fall. This will enable timely fulfillment of updated contracts to provide vaccines for any additional US needs, such as a booster dose in the fall and/or in the first half of 2022. It can also provide significant, relatively short term vaccine supply for global needs. (Additional details are in the Appendix.)

In addition to donations of doses, *loans* of currently available doses (as with Mexico and Canada, see below), or shifts in timing of delivery to prioritize other countries' urgent needs without formal donations (as is reportedly under consideration with Brazil), would offer additional options for bilateral engagement and vaccine access.

The following key principles should drive the strategy and priorities for access and distribution involving this robust manufacturing capacity:

- Allocation and distribution should be [equitable](#), based on the evolving burden from COVID-19 and urgency of need relative to available health resources;
- Each country should have sufficient vaccine supply to protect its own population, while maximizing support for all other nations to do so to end the pandemic as quickly as possible; and
- Timing is critical – countries with excess doses should release them to other countries provided that domestic needs are met, including “manufacturing slot swaps,” which achieves both adequate supply and accelerates availability to help save lives and protect health systems globally.

With a dynamic global pandemic and growing urgency in many parts of the world, now is the time to advance an effective plan for distributing additional excess doses as they become available. This will require modifying existing contracts, to extend similar features like liability protection that are present in US, EU, and other existing production contracts. This should be feasible: the US has reportedly already [“loaned” 4 million doses](#) of the AstraZeneca vaccine to Mexico and Canada; the vaccine is authorized by those countries’ regulatory authorities. In the months ahead, we expect that any US-donated vaccines will meet FDA emergency authorization standards; well-established standards should apply to all vaccines used in the response to the global pandemic. These contracts could serve as a model for further agreements, with financial backstops from the US and other governments, to procure additional vaccines from the enhanced manufacturing capacity that the US has supported.

Vaccine allocation and distribution could occur through three potentially complementary mechanisms:

- (1) **Donation through COVAX:** As the global multilateral platform for COVID-19 vaccine access, COVAX could channel donated doses through its existing population-based allocation framework and infrastructure. COVAX partners have extensive experience deploying vaccines to low-income nations, working with UNICEF, providing one system for advancing equity across the world. However, this model and COVAX’s tripartite governance is untested at scale against a shifting and massive pandemic challenge. Moreover, in its first phase, COVAX is allocating doses primarily based on population. This could help avoid political biases in allocations, but could also result in vaccine allocation that is less effective in controlling the pandemic.
- (2) **Bilateral donations or loans (PEPFAR model):** The US can lead by example through bilateral donations or loans to specific countries. A complementary strategy to COVAX would be to use a bilateral program, modeled on PEPFAR, that would include supplying not just the doses but also technical and managerial support and funding to assure supply and distribution logistics and training of health workers. For HIV and antiretroviral therapy, PEPFAR brought together the range of resources – including USAID, CDC, DoD, and the Peace Corps – to provide the coordinated support required to address local distribution challenges and uncertainty or hesitancy about treatment. Similar assistance now could build on PEPFAR experience and resources.

Factors for consideration in distributing excess vaccines to countries could include: disease burden, capacity of health systems, US ability to leverage existing distribution systems or provide added technical assistance (existing infrastructure, for example through PEPFAR and bilateral immunization programs, could help deliver vaccines and eventually antiviral treatments), and trade and diplomatic considerations (Mexico, Central and South America). The bilateral approach may be particularly important for

efforts to distribute mRNA-based vaccines due to the current cold-chain storage and distribution requirements.

In taking these steps, the US should encourage similar initiatives by other G7 countries that could be implemented in parallel to multi-lateral efforts, just as the US coupled PEPFAR with support for the multilateral Global Fund to Fight AIDS, Tuberculosis, and Malaria. Importantly, bilateral and multilateral efforts should be coordinated such that countries receive the same vaccine from different sources, augmenting distribution capabilities without fragmentation of support.

- (3) **Use of multi-lateral platforms independent of COVAX:** This model would build upon recent announcements regarding the Quad platform to provide financing for additional vaccine manufacturing capacity in the Asia/Pacific region in partnership with India, Japan, and Australia. The US could provide donations of vaccines as well as financing and technical assistance through the Quad and other existing multi-lateral platforms, such as the African Union/Africa CDC joint COVID-19 African Vaccine Acquisition Task Force ([AVATT](#)), and the Africa Medical Supplies Platform ([AMSP](#)), and regional bodies such as the Association of Southeast Asian Nations (ASEAN).

With increasing vaccination and better outbreak control in the US and other high-income countries, the approach used here can facilitate timely redirection of manufacturing capacity to other countries, paving the way to faster global control.

III. Substantially Increase Safe and Reliable Manufacturing Capacity

Increased safe and reliable manufacturing capacity could be implemented through a public-private partnership that includes voluntary licensing arrangements to increase manufacturing capacity, while assuring the transfer and use of the manufacturing-quality know-how needed for timely manufacturing of safe and effective vaccines. An effective partnership would need to be comprehensive: governments working with the private sector would need to address trade practices that complicate access to upstream supplies, and support specialized workforce training, in addition to expediting manufacturing of safe and effective vaccines. In such an initiative, the US government (and other governments) would provide part of the advance financing to ramp up the process, similar to existing contracts.

Such an initiative should aim to assure adequate supply of the raw materials and consumables needed from start to finish in the vaccine manufacturing process. Increased demand for these materials could delay or interrupt vaccine manufacturing as more capacity comes on board. Supply challenges in the manufacturing value chain were identified in a [landscape analysis](#) prepared for a meeting convened by Chatham House on COVID-19 vaccine manufacturing in March 2021. These include cationic lipid particles for mRNA vaccines, bioreactor bags, cell culture

media, filters, and vials. There have already been reports of raw material shortages from manufacturers including [Novavax](#) and the [Serum Institute of India](#). Building on its efforts to strengthen pharmaceutical supply chains, the US could support increased production in ingredients and consumables needed to accelerate global manufacturing capacity, and better awareness and coordination of available production capacity of these items.

Consequently, the initiative would include the following steps for each vaccine involved:

- Rapid assessment of gaps and shortages in global supply chains needed to support increased manufacturing capacity, including fill-and-finish capacity;
- A plan to manufacture and provide adequate, coordinated supply of key ingredients (lipid particles, proteins, vials, etc.), so that additional manufacturing does not divert current supply and create complications in fulfilling existing vaccine contracts;
- Model contracts and US government facilitation and support of additional bilateral or multilateral contracts to scale up vaccine production – for example, modeled on the [Quad Vaccine Partnership](#) arrangement for India’s Biological E to produce 1 billion doses of JNJ and Novavax vaccines by the end 2022, in collaboration with technical guidance and support from the manufacturers; model contracts could support advance purchase commitments to enable standing up additional large-scale specialized mixing machines and supporting processes for mRNA vaccine production, in collaboration with mRNA manufacturers; this effort to collate model contracts could leverage the Master Alliance Provisions Guide ([MAPGuide](#)) from the Global Health Innovation Alliance Accelerator (GHIAA);
- Support for distribution, through contracts with distributors and enhanced support from USAID, CDC, and Department of Defense technical assistance, to assure adequate systems of storage, transportation, and administration (same systems as described above for supporting distribution and use of excess doses),
- FDA engagement to provide regulatory guidance and assurance that any new manufacturing meets appropriate regulatory standards – vaccine manufacturing is extremely complex, and errors could not only cause safety issues but also worsen the pandemic, if vaccines are less effective (e.g. against variants) or less widely accepted;
- No-fault compensation which might be modeled on the COVAX AMC [no-fault compensation program](#), given that such doses would not be covered by the WHO fund;
- Financing support to accelerate public and private investment across the vaccine manufacturing and distribution ecosystem, led by the US International Development Finance Corporation (DFC), potentially in collaboration with the International Finance Corporation (IFC) through its [Global Health Platform](#); and
- Initial multi-year funding with a call and pathway for other nations to contribute.

Like some of the existing bilateral and multilateral contracts, pricing for vaccines to contain the pandemic globally should be at nonprofit levels, but adequate to assure high-quality, safe vaccine

production and distribution, as well as real-world monitoring and research to address variants and other emerging challenges.

Manufacturing could be accomplished either through contracts with existing available vaccine manufacturers and fill-and-finish facilities, as in the Quad arrangement, or through supporting new regional manufacturing capacity, in Africa and elsewhere. Standing up new manufacturing sites may not be as fast, but would support regional economies and reduce storage and transportation costs, and help assure low-cost, safe and reliable capacity in the event that boosters are needed on an ongoing basis. This approach should support enhanced end-to-end capacity alongside a new regional manufacturing site. For example, a “wheel and spoke” model across a region that also includes developing manufacturing capacity for key ingredients like lipid particles and vials, as well as fill and finish capacity, could help align regional support and strengthen regional health systems for the future.

For sustainability, any new manufacturing capacity should not be financed only or mainly through official development assistance, but should involve private investment jointly with public and nonprofit support, with an effective governance structure. For example, for production in Africa, the US could contribute toward needed capital expenditures through the DFC and IFC in collaboration with regional development banks, foundations, and private investors. The US could also provide partial funding for initial advance purchase contracts with incentives for matching, and a commitment for FDA in collaboration with WHO to support a process for tentative approval for the resulting vaccines, as has been done for PEPFAR drugs and other products.

For vaccine distribution, the US could support an extension of the PEPFAR infrastructure – in countries where such infrastructure is strong – to facilitate vaccine distribution. Steps to support vaccine distribution could also be a foundation for enabling distribution of antiviral medications, and for sustainably strengthening health systems and public health infrastructure for the longer term.

Conclusion

The United States has supported the rapid development and production scale-up for multiple safe and highly effective vaccines, along with extensive regulatory oversight to assure that the complex manufacturing processes are reliable and rare adverse events are well understood. These achievements also provide unique resources to support effective “vaccine diplomacy.” The capacity and knowhow that is helping the US contain the pandemic provides the foundation for an effective and timely strategy to help the world do so – an essential next step to assure COVID-19 containment and recovery at home.

Appendix: Methodology for Excess Dose Projections

The projections presented here are based on our best estimates, using limited and dynamic data. We include advance purchase commitments with the US government from five manufacturers (Pfizer, Moderna, AstraZeneca, Johnson & Johnson, and Novavax), and assume that the Novavax vaccine will receive emergency authorization in the second quarter. (The AstraZeneca vaccine and the Johnson & Johnson vaccine have been authorized by the WHO and EU, and at the time of this writing the Johnson & Johnson vaccine has been authorized with use paused in the US.) The excess dose projections were calculated by assessing vaccine demand in the US based on population and supply based on current purchase agreements and production timelines. To calculate demand for adults, we used the [US census data](#) and assumed 75 percent of the population would receive a two-dose vaccine and 25 percent would receive the JNJ one-dose vaccine. With this estimate of total doses needed, we subtracted the number of doses supplied by the end of March (over 200 million doses based on CDC allocation data) to determine remaining potential US demand. To calculate supply, we used purchase agreements for each vaccine to determine how many doses will be available by the end of July, and used current reports of manufacturing capacity to determine monthly production. We compared monthly supply with demand to determine when there would be enough doses to cover all adults and to calculate excess doses per month through July.

Based on latest reports from [Pfizer](#), its vaccine could be authorized for use in children 12-15 by summer. To calculate the number of doses needed to cover this cohort, we used US census data for children 5-17 and conservatively estimated that half of this population would be eligible. We further assumed two doses for each adolescent which would bring the total doses needed to approximately 53 million.

Looking ahead to the fall, we used publicly available information on projected scale-up over the coming months – to project monthly supply. This projection is uncertain given the variables involved in scale-up of each vaccine and the multiple revisions over time for projected capacity.

To estimate number of boosters needed for the fall, we assumed all adults would need an additional dose in the fall, regardless of which vaccine used initially (~260 million doses for all adults and an additional 30 million for children 12 and over). While projections for particular companies are uncertain, based on public statements regarding short-term vaccine supply and fourth-quarter expected capacity increases, we assume that production capacity will be sufficiently enhanced by late 2021 and beyond to provide for vaccinating younger children and to provide additional boosters in 2022.