THE US DID NOT BAN EXPORTS OF VACCINE SUPPLIES. BUT MORE HELP IS NEEDED.

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Just a few months after India confidently promised to send homegrown COVID-19 vaccines to billions of suffering people around the world, local production sputtered and a new wave of disease spread across the country. Indian vaccine makers were forced to keep their limited supplies at home, prompting them to try to shift the blame away from themselves. The most obvious target has been the United States, which the CEO of the Serum Institute of India, the world's largest vaccine manufacturer, accused of imposing an "embargo" on vital ingredients needed to make the vaccine.

That would be a scandal if it were true. But it is not. Access to new, firm-level supply-chain data reveals there has never been a US export "embargo" on materials needed to manufacture vaccines. In recent months, in fact, the Serum Institute and other Indian companies have significantly increased imports of vaccine materials from key suppliers in the United States, including Merck Millipore, Thermo Fisher, Cytiva, Pall, ABEC, Sartorius, and more.

On April 16, Adar Poonawalla, CEO of the Serum Institute, brought things to a head with a tweet. "Respected @POTUS, if we are to truly unite in beating this virus, on behalf of the vaccine industry outside the U.S., I humbly request you to lift the embargo of raw material exports out of the U.S. so that vaccine production can ramp up." He was not alone in accusing the US government of using the Defense Production Act (DPA) to ban exports of supplies. Mahima Datla, the CEO of Biological E, another major Indian vaccine company, made similar public complaints. President Joseph R. Biden Jr.'s national security advisor, Jake Sullivan, responded that the United States would help by immediately sending emergency vaccine-making equipment to India.

There is, of course, enough blame to go around. Vaccines have not been equitably distributed worldwide. Vaccine equipment and materials are in short supply globally, and shortages may even temporarily get worse. The White House was slow to explain that the Defense Production Act was not being used as "an export ban or a de facto ban or an embargo or any restrictions on sales to any other outside clients or customers anywhere. Companies are able to export however they need."

But there is something to be learned from the misplaced accusations of CEOs, if policymakers can raise their sights and focus on helping India and other countries now struggling to expand their immediate vaccine production capabilities. Policymakers should work to provide more transparency into the vaccine manufacturing supply chain to avoid these sorts of misperceptions. More important, they should use that information to partner with companies *globally* to identify and mitigate the worst of the input shortages before the shortfalls stop or slow down vaccine production. The supply chain data presented here can help.

WHAT IS KNOWN ABOUT THE SERUM INSTITUTE, BIOLOGICAL E, AND VACCINE INPUTS

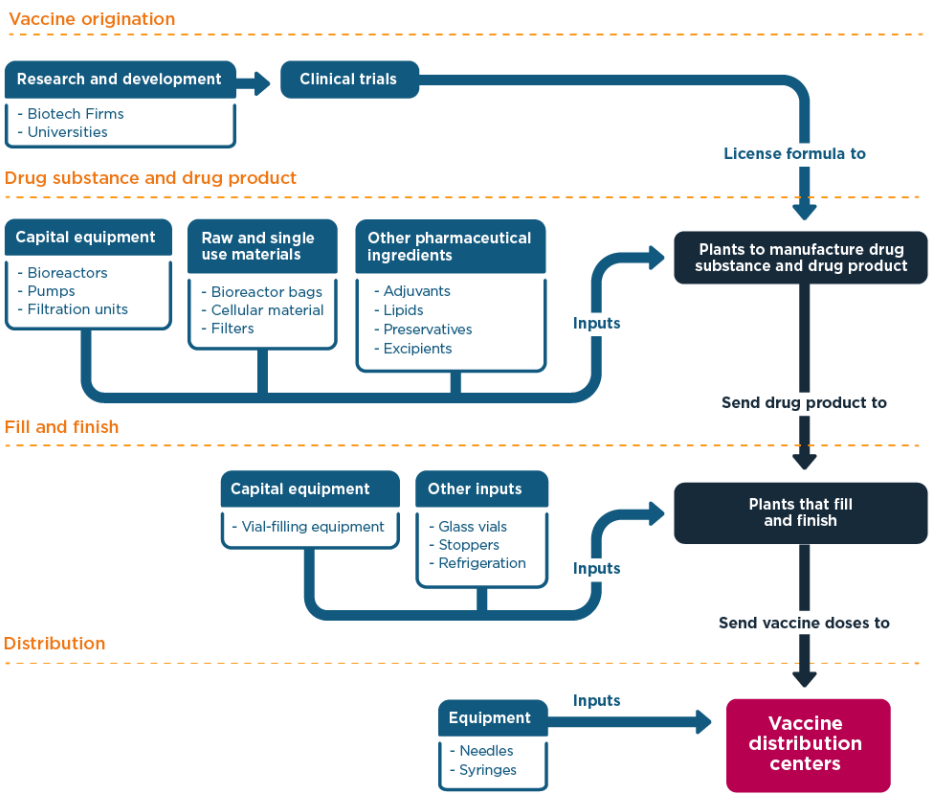
The Serum Institute has licensed technology to manufacture two vaccines – one from AstraZeneca in June 2020 and one from Novavax in July. The company secured funding from Gavi and the Bill & Melinda Gates Foundation in August and September to begin to scale up manufacturing that was at risk – i.e., before regulatory approval of the vaccines. In exchange, the Serum Institute agreed to supply hundreds of millions of doses to poor countries through the COVAX Facility over 2020 and 2021.

Manufacturing a vaccine is complex but can be separated into two basic stages (Figure 1). The first involves making the drug substance and then formulating it into drug product. This requires capital equipment such as bioreactors and filtration pumps but also a continuous supply of "single use" (disposable) materials such as bioreactor bags, filters, and tubing, as well as chemicals and cellular and other raw materials known as "consumables." Once done, a second facility takes shipments of the drug product and uses its assembly lines to squirt liquid vaccine into millions of tiny vials, adding caps and labels, and then packaging them up for distribution.

Figure 1

Vaccine manufacturing is a multi-stage process that often requires extensive collaboration

The stages of vaccine development and manufacturing



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Note: Select stages and inputs depicted illustrate general vaccine production process and are not comprehensive.

Source: Chad P. Bown and Thomas J. Bollyky. Forthcoming. "How Covid-19 vaccine supply chains emerged in the midst of a global pandemic". PIIE Working Paper.

To manufacturer the Novavax vaccine, for example, the Serum Institute procured massive new pieces of capital equipment in September, buying six 4,000 liter bioreactors that ABEC indicated were the "largest in the industry by a factor of two." ABEC would manufacture the bioreactors and customized, single-use bioreactor bags "in its US and Ireland facilities to meet Serum Institute's accelerated schedule." (Nevertheless, ABEC is currently reporting a 16-18 week lead time for new shipments of its bags.)

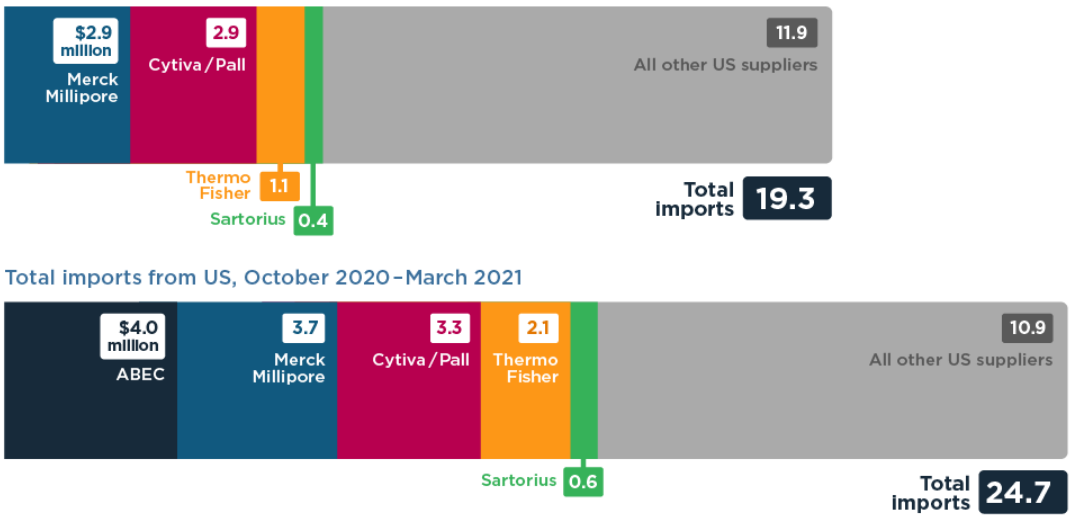
The Serum Institute may have also repurposed legacy equipment already on hand, including to manufacture the AstraZeneca vaccine – which it has called Covishield. In the face of Poonawalla's plea for more equipment, on April 26 the White House announced emergency shipments of "[Merck] Millipore filters that would have been used to manufacture AstraZeneca vaccine that will be used to manufacture the Covishield AstraZeneca vaccine [sic] serum."

Equipment is likely in short supply globally, but there is no evidence to suggest a US "embargo" on Merck Millipore, ABEC, or any other company sending vaccine supplies to the Serum Institute (figure 2). Using S&P Global Market Intelligence Panjiva's (Panjiva) data, which is based on Indian customs transactions, the Serum Institute received $25 million of imports from the United States between October 2020 and March 2021. This volume made up 22 percent of the Serum Institute's imports from the world and was more than 30 percent higher than the prior six months.

Figure 2

India's Serum Institute received more vaccine supplies from US firms between October and March than the previous six months

Serum institute imports from the US by supplier, millions of dollars



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Merck Millipore = EMD Millipore Corporation, Millipore SAS, MilliporeSigma, or Sigma Aldrich International. Cytiva = Cytiva, Global Life Sciences Solutions, or Hyclone Laboratories. Pall = Pall Corporation or Pall Filtration. Thermo Fisher = Thermo Fisher Scientific, Life Technologies Corporation, Life Technologies Holdings, Thermo Scientific, or Thermo Electron. Sartorius = Sartorius Lab Instruments or Sartorius Stedim Biotech.

Note: Entries corrected to drop imports of gold (Harmonized System code 7108.12).

Source: S&P Global Market Intelligence Panjiva.

A number of American-based vaccine equipment suppliers made shipments to the Serum Institute between October and March. In October and December, those 4,000 liter bioreactors arrived, reflecting $4 million of purchases from ABEC. Merck Millipore also shipped $3.7 million of goods, including filters; Cytiva and Pall sent a combined $3.3 million of exports, including disposable bioreactor bags. Serum also imported $2.1 million from Thermo Fisher and $600,000 from Sartorius.[1]

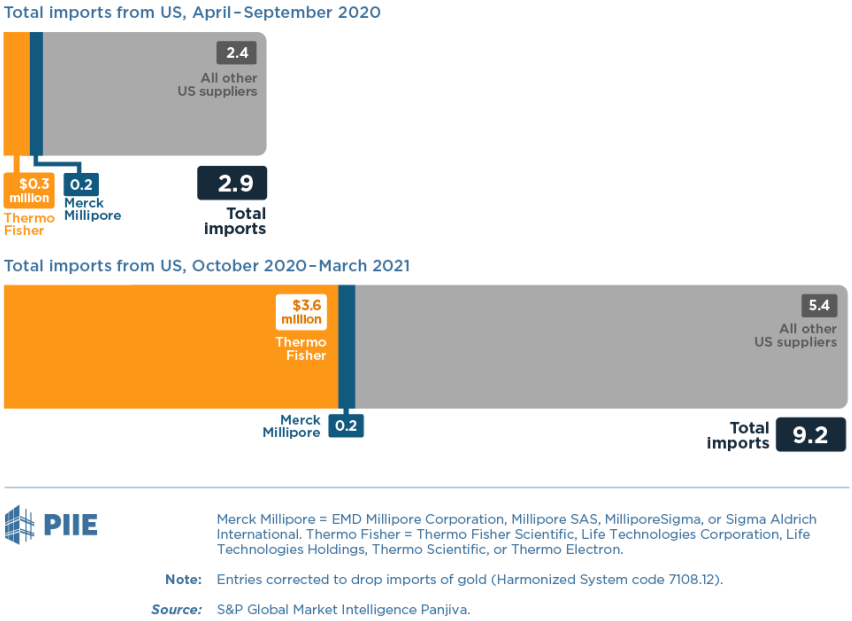
The Serum Institute was not alone. Biological E has been preparing to manufacture two other vaccines – one from Johnson & Johnson (Janssen) as well as one from Dynavax and the Baylor College of Medicine. While Indian regulators have not yet authorized either for use, Biological E has had a technology agreement for each since August 2020.[2]

Biological E shows similar buying patterns from US suppliers (Figure 3). Between October and March, the vaccine manufacturer received $9 million of imports from the United States, 29 percent of its total imports and an increase of 220 percent (from $2.9 million) from the prior six-month period. Thermo Fisher shipped $3.6 million of those goods, including bioreactor bags, and $187,000 of the exports, including filters, were from Merck Millipore.

Figure 3

Biological E received more vaccine supplies from US firms between October and March than the previous six months

Biological E imports by supplier, millions of dollars



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Note: Entries corrected to drop imports of gold (Harmonized System code 7108.12).

Source: S&P Global Market Intelligence Panjiva.

[1] The Serum Institute also imported $85,000 from AstraZeneca for the recombinant vaccine from the UK in September to get things started, and $50,000 from AstraZeneca for reagents from the United States. The company also imported $300,000 from Novavax for its drug substance and over $250,000 for its specialized Matrix M1 adjuvant from the United States and Sweden. The Indian firm also spent $12 million on a new vial filling line from Syntegon in Germany.

[2] Another Indian firm, Bharat Biotech, has been manufacturing COVAXIN, a locally invented vaccine, and has been distributing it under emergency use since January (even though its phase 3 trials were not announced until April 21). Its data is not shown here as it imported little from the United States over the entire period.

The existence of these US exports does not mean, of course, that all of the equipment and materials were to be used to make COVID-19 vaccines. (The Serum Institute and Biological E also manufacture other vaccines.) It also does not imply that these Indian manufacturers are still not missing critical parts or that supplies are not running short. Equipment shortages have been a problem throughout the pandemic, even impacting American vaccine companies. At one point Pfizer, for example, had to recycle individual filters two or three times to avoid running out.

American suppliers of vaccine equipment agree. In a *Bloomberg* interview in January, Chris Ross, CEO of Merck Millipore, indicated the company had been hit with "off-the-charts'' demand for filtration devices and the single-use equipment that their clients needed to make COVID-19 vaccines.

VACCINE MANUFACTURERS GLOBALLY MAY ALL BE RELYING ON THE SAME FEW SUPPLIERS

There are many causes of the equipment and raw materials shortages. But things may have been made worse because of how the supply chains for some of these vaccine manufacturers developed, creating a demand spike for the same materials from the same few companies at the same time.

Take the AstraZeneca vaccine's global manufacturing network. The first stage is now being done by at least nine different companies in eight different countries (Figure 4). The second stage happens in at least ten different facilities in nine countries.

Pall and Cytiva, a pair of subsidiaries under Danaher, are likely supplying at least *some* equipment for the AstraZeneca vaccine supply chain network. Pall was part of the original consortium the Oxford vaccine originators convened in early April 2020 that later expanded to include the AstraZeneca partnership. Clive Glover, Pall's director for cell and gene therapy, described the equipment implications (of Figure 3) with, "The need to standardize was a necessity for this project because there are more than 20 different sites manufacturing [the Oxford/AstraZeneca vaccine], each using the 50 or so consumables required for the manufacturing process. If each site had its own customized version, there would need to be more than 1,000 parts!"

Standardizing the AstraZeneca production process would have tradeoffs. A benefit of common equipment and materials would be the speed at which each new facility could scale up production of a consistent drug product. But the downside of standardization is it may concentrate – and lock in – demand for equipment into a limited number of suppliers. That is, the benefit of that speed and drug product consistency can only be realized if there is enough of the standardized equipment to go around.

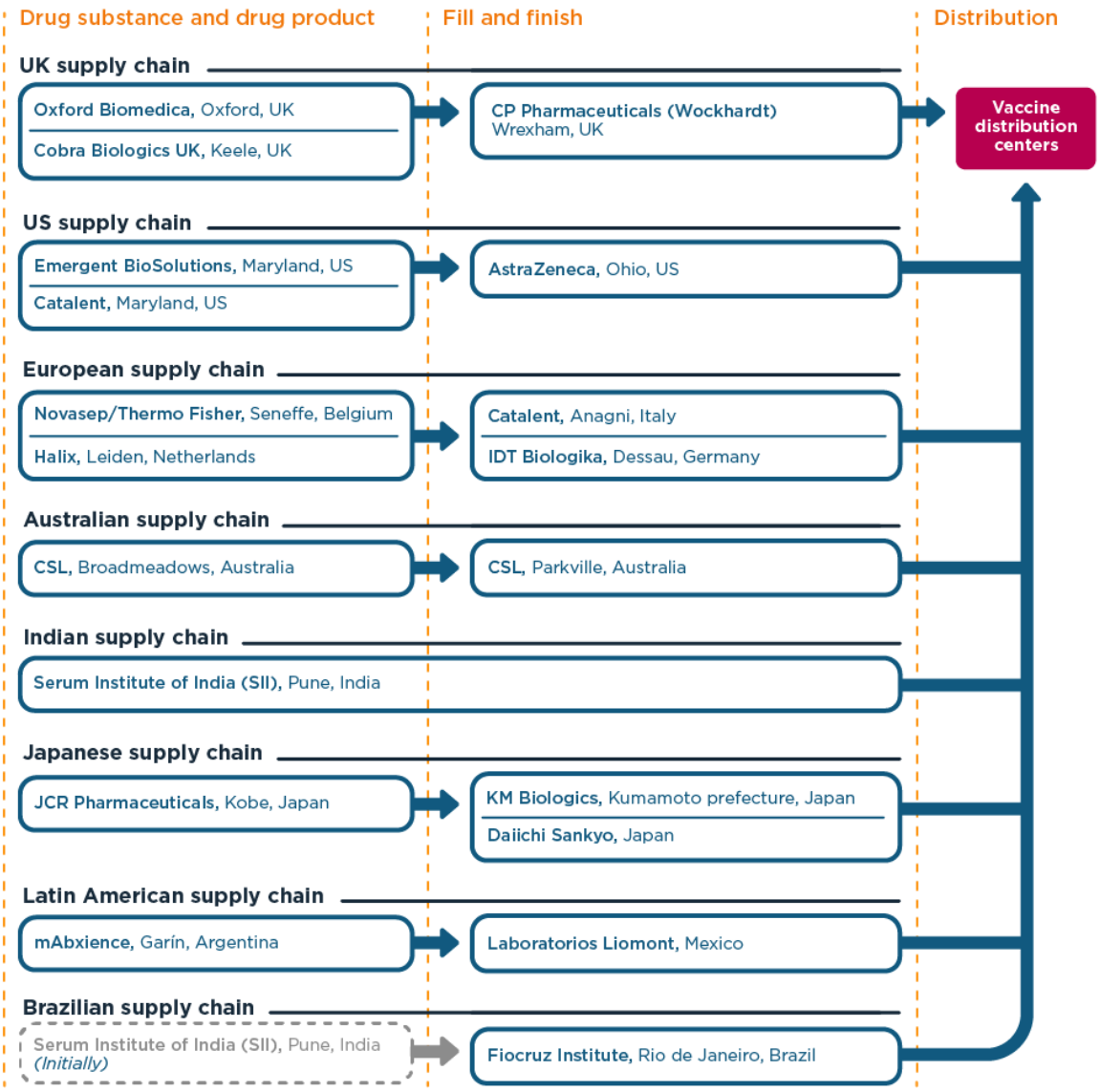
The Serum Institute may face intense competition for equipment from many other sites in the AstraZeneca COVID-19 vaccine manufacturing network. Two US facilities – for Emergent BioSolutions and Catalent – have had AstraZeneca production taking place under a DPA priority-rated contract since summer 2020, giving those plants earlier access to any US-based supplies that the Serum Institute might also need.[3] This may explain how the US government was able to find Merck Millipore filters to share with the Serum Institute on April 26. Finally, demand for equipment to make the AstraZeneca vaccine was also likely coming from newly-tasked facilities in the Netherlands, Belgium, Australia, Japan, Argentina, and the two in the UK (see again Figure 3).

[3] In early April, the Biden administration shut down AstraZeneca operations at the Emergent BioSolutions facility and indicated it would help it find a new plant in the United States.

Figure 4

AstraZeneca's global vaccine manufacturing network

Partners and facilities involved in Oxford/AstraZeneca vaccine production



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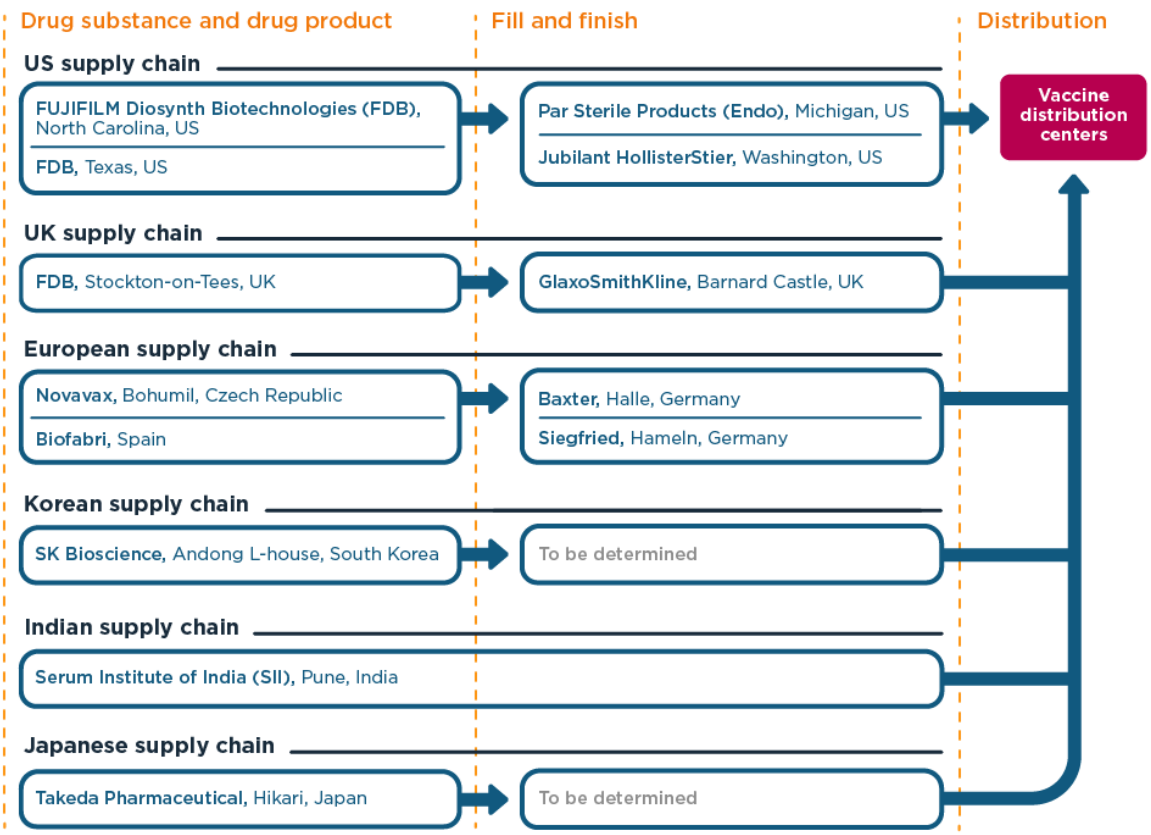
Note: As of June 1, 2021. The Novasep plant in Belgium was taken over by Thermo Fisher in January 2021.

Source: Chad P. Bown and Thomas J. Bollyky. Forthcoming. "How Covid-19 vaccine supply chains emerged in the midst of a global pandemic." PIIE Working Paper.

Figure 5

Novavax's global vaccine manufacturing network

Stages and partners involved in Novavax vaccine production



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Note: As of June 1, 2021.

Source: Chad P. Bown and Thomas J. Bollyky. Forthcoming. "How Covid-19 vaccine supply chains emerged in the midst of a global pandemic." PIIE Working Paper.

A similar uptick in demand for common equipment likely affected the Serum Institute's ability to scale up production for Novavax. Novavax has contracted at least seven other facilities to manufacture the drug product for its vaccine (Figure 5). Two are in the United States, and at least one of them, Fujifilm Diosynth Biotechnologies (FDB) in Texas, also appears to use equipment from Pall and Cytiva.[4] The other Novavax facilities are in the UK (also a FDB plant), Czech Republic, Spain, Japan, and South Korea. In April, Novavax CEO Stanley Erck indicated some facilities were threatened by a global shortage of bioreactor bags, but he did not indicate which plants or which supplying companies were behind the shortfall. Finally, note that the Emergent BioSolutions plant also had the ABEC 4,000 liter bioreactor in place prior to the pandemic. (Other COVID-19 vaccine efforts were reportedly also using ABEC

[4] A job opening for a "Manufacturing Supervisor" indicated the position required operational oversight of various systems including "single use mixing systems (Pall & GE)" – where "GE" refers to GE Healthcare and is now Cytiva.

equipment.) Thus, many facilities were likely competing with the Serum Institute for bags and other materials needed to make the Novavax vaccine.

The shortages were predictable, and under Operation Warp Speed, the US government at least attempted to address the problem. In October, it provided Cytiva $31 million to "expand manufacturing capacity in the company's Massachusetts facilities and create duplicate capabilities in Cytiva's Utah facilities to be complete in less than 12 months." To help it scale up faster, Cytiva was also given priority access to input suppliers through an invocation of the Defense Production Act.

The US government subsidized Cytiva in part because it was "the primary supplier to *many of the companies* currently working with the U.S. government to develop COVID-19 vaccines" (emphasis added). But even if the subsidies to Cytiva were sufficient to expand the input capacity needed to satisfy American vaccine manufacturers, they were unlikely to have been large enough to satisfy the surge in global demand.

A NEW AND GLOBAL COVID-19 VACCINE SUPPLY CHAIN POLICY IS NEEDED

The challenge facing policymakers today is different from what it was six to twelve months ago. Then, US policymakers were focused on securing the American vaccine supply chain. At that point, which vaccines would receive regulatory approval remained unknown. Now, dozens of facilities making vaccines for Pfizer, Moderna, Johnson & Johnson, AstraZeneca (Figure 3), Novavax (Figure 4), and more have all been established *globally*. Furthermore, as the Indian trade data confirmed, these facilities have already formed relationships with critical equipment and raw material suppliers around the world.

Today, policymakers need to leverage information about those relationships to identify and resolve potential input shortages *before* they stop or slow the much needed expansion of COVID-19 vaccine production. Here are five steps explaining how to do so (Figure 6).

1. Regularly survey the dozens of now-established COVID-19 vaccine production facilities about their critical inputs.[5] How much do they need, from which companies, from where are those being supplied, and on what time schedule? Furthermore, how customized is each input? (Is it truly unique to that supplier?)

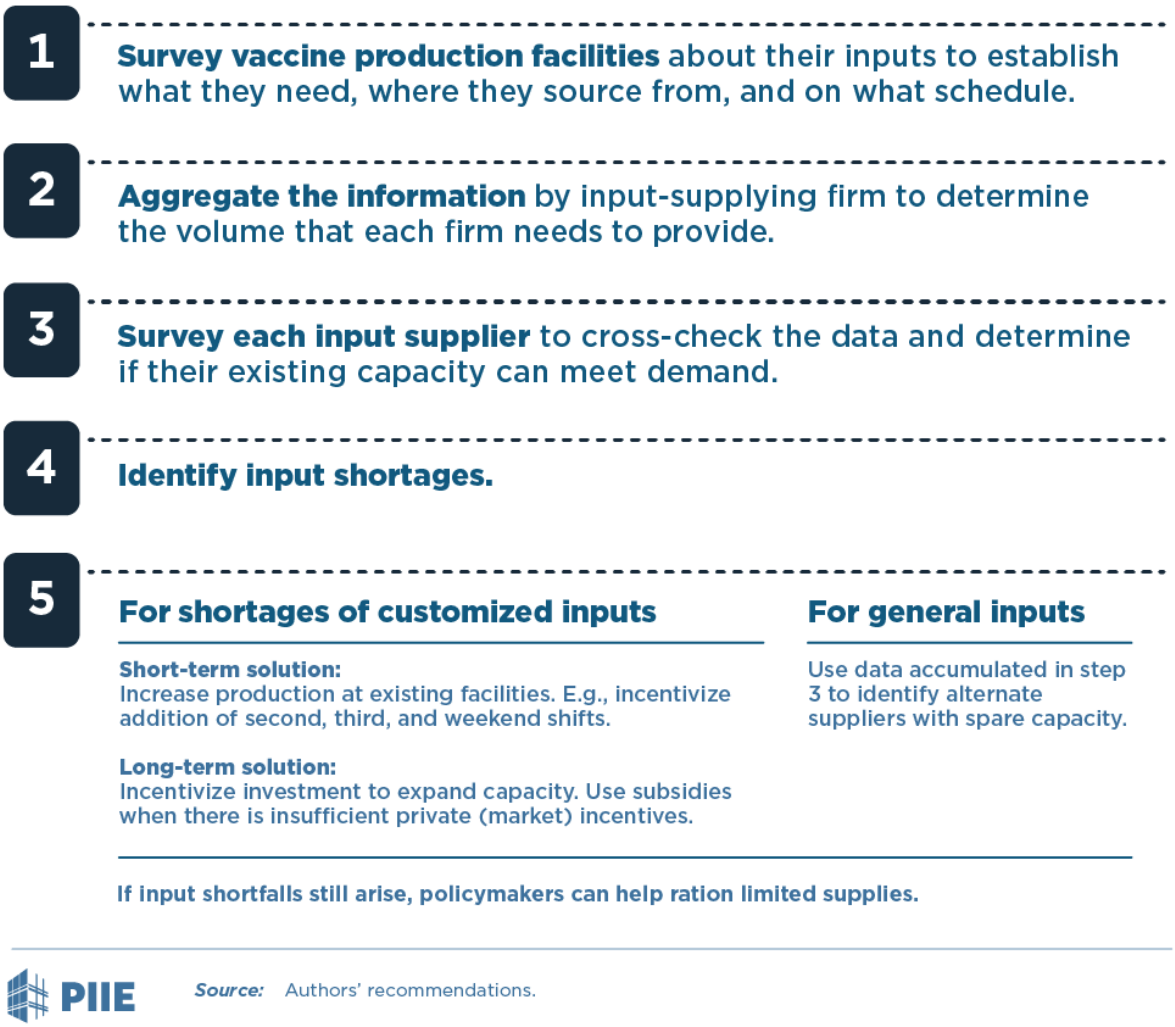
2. Once that information has been collected for each facility, aggregate it up to the level of the input supplier. Determine how many bioreactor bags are needed from Cytiva versus Thermo Fisher. Establish how many filters are needed from Merck Millipore, etc.

[5] A database of the facilities for vaccines from Pfizer, Moderna, AstraZeneca, Johnson & Johnson, Novavax, and Curevac as of June 1, 2021, can be found in Chad P. Bown and Thomas J. Bollyky, forthcoming, *How COVID-19 vaccine supply chains emerged in the midst of a global pandemic*, Peterson Institute for International Economics working paper.

Figure 6

How to use supply chain transparency to minimize COVID-19 vaccine input shortages

Five policy steps to stop shortages of inputs from slowing vaccine production



PIIE *Source:* Authors' recommendations.

3. Separately survey the major input suppliers identified in step 2. Cross-check whether each input supplier's pending orders match the information from the vaccine facilities. Check other competing claims on that input production (from clients making products aside from COVID-19 vaccines), and establish whether their existing capacity can satisfy orders from COVID-19 vaccine facilities on time. Can Merck Millipore really meet the simultaneous new demand for filters from Serum Institute, the Novavax plant in Texas, and the AstraZeneca facility in the Netherlands? Will Cytiva have enough bioreactor bags to service all of the plants in their order book? If a plant really needed more of this particular piece of equipment or raw material, would Thermo Fisher have any spare capacity to provide it?

4. Identify potential input shortages. Whenever step 3 reveals a supplier as not having sufficient capacity to meet all of the demand on time, some sort of policy intervention is needed.

5. Determine whether the shortage is impacting a customized input, and tailor the policy response accordingly.

For customized inputs that no other equipment supplier can make, there are two possibilities. Policy should first incentivize the company to utilize its existing capacity more intensively, in a wartime-like-effort, running second, third, and weekend shifts.

If that resulting increase in production of equipment and materials remains insufficient, incentivize the capital investment necessary for that company to expand productive capacity to provide more of those customized inputs.

Even with current heightened demand, an input supplier may not have the private incentive to invest in new capacity if it perceives that demand as transitory. For example, a private company may perceive facilities manufacturing pandemic-specific equipment, such as huge bioreactors or their enormous single-use bags, as having limited utility once the health crisis is over and tens of billions of vaccine doses are no longer a global regularity. Society needs companies to make this capacity investment right now to save lives, and governments may have to pay for it with subsidies. The evidence is that the industry is making large capital investments.[6] But without the policy intervention, private firms might not make the *right* expansions into pandemic-level capacity to address the public health crisis.

For inputs that are not customized, use the step 3 information to help find temporary alternative suppliers. Take advantage of the information on spare capacity collected by having surveyed the other input providers.

Even following this checklist, sometimes there will be no immediate way to resolve an input shortage. In this case, policymakers can use the information they have collected on global production to help ration and nudge supplies to where they can do the most public good. Nevertheless, the pace of vaccine production will slow.

MAKING OPERATION WARP SPEED GLOBAL

US policymakers have arguably deployed elements of this five-step process during the pandemic on behalf of American vaccine makers through Operation Warp Speed and the Defense Production Act. And when vaccine facilities in other countries have run into equipment shortages, the US government has sometimes even stepped in to help, as with the Serum Institute in April as well as with CureVac in May.[7] But the Indian experience showcases why the United States cannot and should not attempt to manage this five-step process alone. The worldwide nature of the pandemic, as well as the international supply

[6] As *BioProcess International*, an industry publication, reported in May, "All the big vendors have responded to the demand by expediting investment projects or upping their capital expenditures," including Pall, Cytiva, Thermo Fisher, and Merck Millipore. Less clear is what exact capacity expansions these vendors are investing in.

[7] Since March 2021, when Presidents Biden and Ursula von der Leyen appointed Jeffrey Zients and Thierry Breton to address any trans-Atlantic vaccine supply chain challenges, the United States and European Union have been doing this at least informally.

chains characterizing vaccine production and input-providers, means that the coordinated and informed allocation of scarce supplies must take place through a more global lens.

These are some of the now practical and real-world reasons why Bown and Bollyky (2021) have called for a COVID-19 Vaccine Investment and Trade Agreement (CVITA). Coordinating public investment to expand critical inputs and raw materials is required simply because those vaccine supplies may be produced in one country (such as the United States) even though they are desperately needed by a vaccine manufacturer in another (such as India). In the face of input shortages, policymakers may need to step in and make hard decisions about how to best allocate those supplies on behalf of public health. But the public also needs to see those policymakers as making informed decisions.

Transparency in the global vaccine supply chain will also improve trust. That may heighten cooperation and be a reminder that, in the COVID-19 pandemic, we are all in this together.