Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Building the global vaccine manufacturing capacity needed to respond to pandemics

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Among the most pressing issues in preparing for the global response to a pandemic are the design, development, manufacture, and dissemination of vaccines. In 2018 and 2019, we conducted 48 interviews with prominent leaders in public health, pandemic preparedness, vaccine design, and vaccine manufacturing about how they would respond to a sudden, urgent need to manufacture 2 billion or more doses of vaccine. Little did we know that this scenario would become a dire global challenge a few months later with the onset of COVID-19. The response to this pandemic has shown that when leading vaccine manufacturers are fully engaged in a global response, it might be possible for them to manufacture substantial doses of vaccine on timelines faster than previously envisioned. It is now hoped that hundreds of millions of doses of vaccine will start to be produced sometime in the end of 2020 or the start of 2021, and that billions of doses of vaccine could be produced in the months that follow. Whether these timelines can be met or not, it is crucial now, while the world is fully attuned to the terrible consequences of pandemics, to begin preparing the system of global manufacturing for future pandemics. The following insights and recommendations are taken from our interviews with leading experts and our own analysis.

Vaccine manufacturers are best prepared to confront an influenza pandemic, among known biological threats. The influenza vaccine is produced annually at scale through a consistent platform, allowing manufacturers to quickly ramp up production to billions of doses. As of 2015, high-income countries had the capacity to produce 1 billion seasonal influenza vaccine doses each year, while upper-middle income countries could produce 250 million doses and lower-middle income countries could produce 200 million doses. In the event of a pandemic, manufacturers could scale up production to 6.4 billion doses of pandemic influenza vaccine active pharmaceutical ingredient (API) within 12 months. Some experts we interviewed were skeptical that this number could be met in practice. Even if so, it would fail to meet the WHO Global Action Plan for Influenza Vaccine goals, which calls for 70% of the global population to receive two vaccines within six months [1,2].

Manufacturers are far less prepared to address novel threats. At the time of our study, most experts doubted that manufactures could scale up a novel vaccine on a timeline to adequately confront a catastrophic pandemic. Policymakers can adopt four approaches to expand vaccine supply in the event of a pandemic: stockpiling vaccines in advance of an outbreak; reserving excess manufacturing capacity for surge production; financing construction of new manufacturing capacity before or during an outbreak; and repurposing existing manufacturing facilities to produce a pandemic vaccine. Before COVID-19, experts believed these approaches could provide only a modest expansion of capacity within the first 12 months of a novel pandemic.

We will learn an enormous amount from the policies, technologies, and financing strategies used to produce COVID-19 vaccines. Those lessons will be critical to inform emergency global vaccine manufacturing efforts in the future. To that list of lessons, we would add the following four recommendations from our study completed just before the start of COVID-19.

1. Expand the vaccine development paradigm: substantially expand research and development in platform technologies, and other technologies which could allow rapid development and manufacture of medical countermeasures (MCMs) for pandemic response.

Platform technologies – in which a common mechanism, device, delivery vector, or cell line can be employed for multiple vaccines – enable manufacturers to rapidly scale and transfer between biologic MCMs, especially vaccines [3]. By delivering a range of products using the same production mechanism, they may allow regulators to approve products by platform rather than by product. Some platform technologies will improve pandemic readiness more effectively than others: nucleic acid vaccines, for example, may be easier to manufacture quickly than viral vector vaccines. Proven, traditional vaccine development processes will remain a critical part of the response to an emerging pandemic, and it is possible those approaches will succeed where novel approaches do not. But it was clear in our interviews – and is quite clear now in the COVID-19 response – that new approaches could substantially improve surge production capacity and should become a major focus of pandemic vaccine preparation efforts for the future.

2. Encourage flexible manufacturing to overcome limitations resulting from manufacturing specialization

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Many vaccine manufacturing facilities specialize in the production of a single product. This approach arguably maximizes efficiency and economies of scale [4]. However, specialized manufacturing is traditionally inflexible. Flexible manufacturing techniques enable production facilities to switch more rapidly between products, scale up production, or relocate production capacity.

Technologies for flexible manufacturing include single-use components for all stages of manufacture (production, processing, and fill-and-finish), modular factory design, portable modular manufacturing, and continuous processing. Some of these techniques are already in commercial use; others are in development. Modular facilities allow manufacturers to customize continuously and to reconfigure equipment to accommodate new products or processes [5]. Portable modular manufacturing suites could be remotely deployed in a crisis and provide new options for geographic diversification and facility reconfiguration. However, many vaccines currently in use are manufactured using outdated technologies. Influenza and yellow fever vaccines, for example, are still manufactured in chicken eggs, a technique developed in the 1940s [6]. The vaccine industry lags behind other biopharmaceutical production areas as it struggles to increase efficiency in a cautious and demanding market environment. By contrast, monoclonal antibody production has successfully scaled up modern, efficient, and flexible manufacturing processes.

3. Increase vaccine production flexibility and access globally through localized distributed manufacturing

Traditionally, pharmaceutical products are manufactured at scale in centrally located sites. Centralized production provides economies of scale, but it also results in single points of failure in vaccine supply chains and geographic concentration of production. The majority (~80%) of vaccines are manufactured by five large pharmaceutical companies in the US and Europe: GlaxoSmithKline (USA), Merck (USA), Novartis (Switzerland), Pfizer (UK), and Sanofi Pasteur (France) [7]. Thus many regions lack significant vaccine manufacturing capacity, and are often the areas where vaccines are needed most, due to higher prevalence of endemic diseases or heightened risk of outbreaks.

Distributed manufacturing, in contrast, produces final products close to the end user. Advances in DNA/RNA synthesis, 3D printing, mini-labs, and product design would make distributed manufacturing feasible for a wider range of vaccines around the world. Many of these technologies would enable not only decentralized production but also the flexibility to rapidly transition between different product lines. A new regulatory approach would be needed as well, combined with processes for local testing and quality assurance. Vaccine companies would need to share IP in new ways for their products to be produced in a distributed way. Implemented at mass scale, distributed manufacturing could provide not only value for routine use but also benefits for pandemic response. Routine units could switch to provide emergency capacity during a pandemic immediately following regulatory approval. Although distributed manufacturing is unlikely to match the economies of scale afforded by centralized production soon, advances in distributed manufacturing could expand options for rapid, flexible production of vaccines for frontline workers or at-risk populations.

4. Prepare measures to reduce timelines associated with regulatory requirements

Regulatory changes could help facilitate the above capabilities. For example, in the US, the Food and Drug Administration (FDA) currently approves most vaccines by indication. This arrangement typically requires full FDA approval or Emergency Use Authorization (EUA) for new vaccines if they share a common platform but target different diseases, even when the two constructs differ by a single gene [8]. This process helps ensure product safety but slows approval for products that share a platform.

Where feasible from a safety perspective, alternative FDA review strategies might accelerate development, production, and dissemination of novel vaccines. For example, the FDA could consider regulating some technologies by platform, rather than by individual product, accelerating the safety component of the review, perhaps with expedited review processes for new indications. Indeed, the FDA already uses this approach with the seasonal flu vaccine.

The FDA is already providing substantial flexibility in its review of COVID-19 MCMs. Many COVID-19 vaccine trials, for example, are combining or overlapping phases [9]. While accelerated regulatory processes can enable critical flexibility in an emergency, these benefits must be weighed against safety concerns and public trust.

1. Conclusion

COVID-19 was met with insufficient global planning and investment in vaccine surge capacity. Companies and governments around the world are now undertaking substantial efforts to accelerate emergency manufacturing of a COVID-19 vaccine. It will soon be clear how rapidly these combined efforts can produce the quantity of quality vaccine that the world needs. It will be crucial to evaluate this experience as the world prepares for future biological threats.

As part of preparatory efforts, the global community should consider concerted investment in platform vaccine technologies, acceleration of flexible manufacturing capabilities, development of flexible distributed manufacturing technologies, and new regulatory approaches to facilitate these advancements. These investments and innovations would better prepare the world for future pandemics and improve equitable access to vaccines around the world.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Richardson reports being a shareholder or investor in Catalyst Pharmaceuticals; Moderna, Inc., and in broadly diversified stock market index funds, which include shares in pharmaceutical companies. Daniel Gastfriend reports owning shares in broadly diversified stock market index funds, which include shares in pharmaceutical companies. Nancy Connell reports being a shareholder or investor in Johnson & Johnson, Pfizer and Novartis.

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