CASES IN GLOBAL HEALTH DELIVERY

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Building the Supply Chain for COVID-19 Vaccines

Mid-April 2020 saw a rapid escalation of the COVID-19 pandemic. In the four months after December 2019, when the novel coronavirus that causes COVID-19 was first detected in Wuhan, China, the virus had infected several million people globally, with more than a hundred thousand confirmed deaths (see **Exhibit 1** for daily confirmed deaths by country). China and Italy experienced major outbreaks early and saw hospitals flooded with COVID-19 patients, causing major shortages of vital intensive-care materials. To forestall the overburdening of health care resources, more than a dozen major countries imposed strict lockdowns to slow the spread of the disease, or "flatten the curve" (see **Exhibit 2** for a map of government responses). Government lockdowns disrupted supply and demand in vital industries including retail, tourism, manufacturing, and services, crippling the global economy. As the massive scale of the crisis became apparent, financial markets began to collapse during February, leading some experts to warn of a potential next Great Depression and governments to announce unprecedented rescue packages to contain the destructive economic impact of the crisis.

As governments navigated trade-offs between economic and public health outcomes, a global race had begun for the rapid discovery, production, and distribution of a safe and effective vaccine. The organization of supply chains to manufacture, distribute, and administer a vaccine to a sufficient portion of the 7.6 billion world population to contain the disease, a concept termed "herd immunity," posed significant challenges. Approximately 5.6 billion people needed to be inoculated to achieve that goal. Merck & Co. CEO Kenneth Frazier remarked, "[P]eople are talking about the scientific conundrum of coming forward with a vaccine that works. In some ways, maybe even a harder problem is … distribution. None of us are safe until all of us are safe, so it's got to be given broadly to humanity. We need a vaccine that we can make and distribute around the world."[1] Yale University physician and sociologist Dr. Nicholas Christakis observed, "I think, even if the vaccine or several vaccines are invented in the next few months, which is likely, we still have challenges in manufacturing, distributing, and persuading the public to accept the vaccine."[2]

The pharmaceutical industry typically identified a vaccine proven to work in clinical trials and then built plants to produce it at scale, a years-long process. The world didn't have years, so factories were being built speculatively for the most promising vaccine candidates. Shortages of apparently minor components, such as glass vials and syringes, could impede this process. By November 2020, there were multiple types of

Prof. Marshall Fisher, Kateryna Kharenko, Canberk Ucel, and Prof. Prashant Yadav prepared this teaching case for the purpose of classroom discussion rather than to illustrate either effective or ineffective health care delivery practice.

vaccine candidates with varying manufacturing and distribution requirements. The supply chain that supported vaccines extended from the manufacture of vaccine contents to storage and packaging of components and cold chain transit (the term applied to the transportation of pharmaceuticals). Many experts predicted at the time that the first vaccines approved for public use would likely be only partially effective against infection, so to fully resolve the crisis governments and industry would need to plan for flexibility in manufacturing and distribution systems and to continue to invest in further development beyond the first generation of vaccines.[3]

Vaccine Development Efforts

The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020. By November 2020, vaccine development for COVID-19 had progressed faster than any historical precedent, reflecting unprecedented levels of collaboration between governments, international organizations, research institutions, and companies large and small.

Typically, vaccine research and development, including failed vaccine candidates, involved tremendous costs, ranging from USD 200 million to USD 500 million per vaccine.[4] Fewer than 10% of those that began preclinical trials eventually received regulatory approval.[5] For COVID-19, lavish public and private financing, research grants, and advance purchase commitments by governments and international organizations de-risked the costly vaccine development effort, allowing vaccine developers and manufacturers to rapidly explore, test, and build manufacturing capacity for many vaccine candidates, some using novel vaccine technologies never before licensed for human use. To speed up testing for promising candidates, several clinical trial steps typically conducted in sequence were combined or conducted in parallel. To accelerate distribution once a candidate was approved for commercial use, large manufacturing capacity investments were being made for the most promising candidates.

The key international initiative, termed COVID-19 Vaccine Global Access (COVAX) Facility, was aimed at pooling participating countries' resources to support vaccine development and later provide subsidized access to lower income countries. COVAX Facility aimed to secure by the end of 2021 two billion doses of vaccine to be distributed among all participating countries irrespective of income levels.[6] Co-led by three prominent international organizations with relevant capabilities—Gavi, an international organization aiming to increase access to vaccines in poor countries, the Coalition of Epidemic Preparedness (CEPI), a foundation working to finance and support vaccine development against emerging infectious diseases, and the World Health Organization (WHO)—the initiative numbered among its participants 183 countries representing 93% of the world's population. As of November 16, only the United States (US) and Russia remained outside the program.

The US had since March been spearheading its own initiative, termed Operation Warp Speed, which had allocated nearly USD 10 billion in public funds to support vaccine development and manufacturing efforts. Beyond COVAX and Operation Warp Speed, many countries had engaged in individual deals supporting promising vaccine candidates through research grants and advanced purchase agreements.[7] This search had yielded a global portfolio of some 321 vaccine candidates by early fall 2020, 54 of which had begun human trials by mid-November. Four promising candidates had progressed well into the final stage of large-sample clinical trials known as Phase III (see **Exhibit 3** for the global vaccine portfolio by stage).

Process Overview and Status

Vaccine development typically involved three stages conducted over several years: research (exploratory phase), usually extending two to four years; testing (pre-clinical—using tissue or cell cultures

and animals—and clinical trials, potentially resulting in approval by regulators); and manufacturing (see **Exhibit 4** for vaccine development timelines).

There were three phases of clinical trials within the testing stage. Phase I clinical trials, which involved 20–80 subjects under controlled conditions and careful monitoring, assessed safety and type and extent of immune response in human subjects as well as dosage, schedule, and method of delivery. Promising candidates moved into Phase II trials, which involved several hundred individuals in a more rigorous evaluation of safety and effectiveness with more statistically exacting placebo controls. Phase II trials also often assessed the commercial appeal of a vaccine before moving on to vastly more expensive Phase III trials involving tens of thousands of human subjects.[8]

By October 15, six months into the crisis, 137 COVID-19 vaccine candidates were in pre-clinical trials, with 46 under human trials.[9] This constituted a vast acceleration of typical vaccine processes (see **Exhibit 5** for a historical comparison). To speed development, Phase II trials of COVID-19 vaccine candidates were largely bypassed or combined with larger scale trials. Experts forecasted clinical trials for an initial COVID-19 vaccine to be completed within eight months, compared to the historical average of 9.4 years for complex vaccines (see **Exhibit 3** for a list of candidates likely to be approved in October, 2020.**)** Such accelerated development of vaccines was enabled by years of previous research, large funding that allowed firms to run multiple trials in parallel, and regulators prioritizing COVID vaccines in their evaluation over everything else.

Challenges in Clinical Trials

Because coronavirus was a novel pathogen for which little information was available on incidence rates, variations in severity, and asymptomatic transmission, trial design and stopping rules were more difficult to formulate and effectiveness more difficult to demonstrate. Placebo trials involved randomly assigning subjects to treatment and control groups, the former injected with the vaccine candidate, the latter with a harmless substance not containing the vaccine candidate. Subjects then returned to public life, and the groups were later compared in terms of the proportion that had developed the disease or exhibited asymptomatic infection.

But public health measures like social distancing and the use of face masks complicated this process by reducing the attack rate (i.e., the proportion of a population that contracted the pathogen), which had, in any case, proved to be relatively low for COVID-19, estimated at around 1%. The low attack rate meant that even with large-scale trials with tens of thousands of human subjects, only a small proportion of the subjects would eventually contract the virus and allow testing of the effectiveness of a vaccine candidate. A common approach employed to address this issue was to continue enrolling subjects in clinical trials until enough had become infected to establish statistically rigorous comparisons between treatment-vaccine and placebo-control groups.

Phase III trials for COVID-19 commonly involved around 40,000 subjects, about 20,000 in each group. Given a 1% attack rate, 200 subjects in each group would be expected to become infected over time. Of those, only perhaps 80% would develop symptoms of varying severity; thus, 160 individuals in the placebo group would be expected to become symptomatically infected. Given a hypothetical 100% effective vaccine, no one who received it would develop the disease. The statistical test to establish the effectiveness of a 100% effective vaccine would compare a rate of 0.8% (160 / 20,000) for the placebo group with 0.0% (0 / 20,000) for the treatment group. That difference was only loosely statistically significant.

To establish a statistical difference between vaccinated and control groups would become even more difficult when testing for protection against the relatively rarer severe COVID-19 infections. COVID-19

studies completed by October 2020 suggested that approximately 20% of infected individuals could be expected to develop severe symptoms, rendering the comparison between 0.2% (20,000 * 1% x 20% / 20,000) and 0% given a sample size of 20,000 subjects in each group. A 50% effective vaccine, the U.S. Food and Drug Administration's (FDA's) threshold for approval, would further narrow this difference, making it even harder to establish statistical significance.

For example, in early November, Pfizer-BioNTech's Phase III trial with approximately 44,000 subjects had revealed its vaccine candidate to be over 90% efficacious. Although encouraging, the results did not estimate the effectiveness of the vaccine to prevent infection or to reduce transmission. That would require many more subjects.

Politics and the Temptation to Rush through the Science

Increasing economic and political pressures threatened to tempt governments to approve vaccine candidates prematurely. A politically-motivated release of an ineffective or unsafe vaccine driven by pre-pandemic global trends towards populism, nationalist politics, and anti-democratic governance could shake the trust of a public already skeptical of the value of vaccination.[10]

Still outside the COVAX initiative, experts worried that the upcoming US presidential elections in November might create an incentive for the administration to push for release of a vaccine before the elections without waiting for the full results of clinical tests.

The tendency towards premature approval had been more apparent in some countries. Russia, the other country that had elected to remain outside of the COVAX initiative, announced early approval, without waiting for the results of conventional clinical trial processes, of a vaccine called Sputnik 5. The August announcement was later rolled back, and large-scale clinical trials were continued.[9] China, which joined COVAX in early October, had approved a vaccine in late June, without waiting for large-scale clinical trial results.[9]

Rushing manufacturing and distribution by skirting time-consuming quality assurance protocols and safety checks could jeopardize already fragile public trust in vaccination programs. Proper manufacturing quality assurance systems insured the safety and effectiveness of each dose.

Vaccine Technologies and Portfolio Diversification

The global portfolio of COVID-19 vaccine candidates involved a diversity of platforms, from well-established to novel technologies not previously licensed for use with humans. Despite the large diversity of first-generation vaccine candidates, there were concerns over politically-motivated exclusion of certain candidates from broader financial and regulatory support, as well as potential incentive issues with large public investments in early-movers.[5] For example, Operation Warp Speed had excluded Chinese and Russian vaccines from its portfolio of investments, potentially compromising the success of its portfolio should one of the excluded vaccine candidates prove effective and safe. Moreover, large bets placed by Operation Warp Speed, COVAX, and individual governments on a handful of initial promising candidates developed by early-movers, including several developed by the large pharmaceutical companies, could divert resources from more promising vaccine candidates further behind in development.

Because ethical standards required that a vaccine candidate approved for broader use be given to individuals in the placebo groups in clinical trials, approval of the first COVID-19 vaccine could slow clinical trials and delay regulatory approval processes for other vaccines. Given the limited production

capacities for each vaccine candidate, delay in approvals of subsequent COVID-19 vaccines could translate to continued suffering and more deaths.

Challenges in Developing Second-generation Vaccines

Consensus among experts that a vaccine released by the end of 2020 or early 2021 would likely provide only partial protection against the disease or may not be suitable for global distribution suggested that development of a more effective second-generation vaccine would likely be needed to fully resolve the crisis.[5] Because discovery, production, and distribution of a second-generation vaccine, whether entirely new or an update of one of the candidates, was expected to take until September 2023,[5] public health measures like social distancing and mask wearing would likely need to be continued, and the economy would continue to suffer, even after distribution of a safe and effective first-generation vaccine. Notwithstanding large bets placed on promising early candidates, continued investment would be needed in further development, and markets would have to be kept functioning and open to new entrants. Concerns had been raised that a partially effective first-comer COVID-19 vaccine could crowd out the market for more effective vaccines further down in the pipeline.

Manufacturing

Manufacturing capacity was typically created after a vaccine candidate had proven effective in Phase III trials. Investing in manufacturing capacity in parallel with trials required companies to build facilities and purchase supplies for a vaccine that could fail in clinical trials; without public financing support, firms were likely to underinvest in the capacity needed to produce large quantities of vaccine rapidly and might also hesitate to scale up manufacturing in a timely fashion. Consequently, governments in the US, UK, and EU and COVAX made advance purchase commitments and provided grants to incentivize vaccine developers and manufacturers to undertake costly investments for the most promising vaccine candidates under clinical trials.

Process Overview

Traditionally, building manufacturing capacity for a safe and effective vaccine took nearly half a decade, two to three years to build the manufacturing plants and as many more to produce in large quantities. Most existing vaccine production capacity was devoted to seasonal vaccines (e.g., for flu and chickenpox). Vaccine developers in developed countries were also finding niche markets for more advanced vaccines for diseases like HPV.

Vaccines currently in use were mostly based on well-established production processes. Production involving embryonated eggs had suffered from unpredictable yields and long lead times, disallowing fast response to surges in demand—let alone a pandemic outbreak. Flu vaccine producers, for example, failed to meet even small demand surges from year to year.[12] Though manufacturing, storage, and distribution processes varied with vaccine, most manufacturing facilities for conventional vaccines were fungible, able to produce other vaccines with some, albeit potentially costly, adjustment.

Vaccine manufacturing involved many complex biological processes coupled with time-consuming quality control procedures to ensure product effectiveness and safety (see **Exhibit 6** for a list of factors impacting manufacturing variability).[13] Testing and quality assurance procedures accounted for approximately 70% of production time. Although manufacturing processes varied significantly across technology platforms, the production process consisted principally of two stages: (i) drug substance

production, which involved producing the contents of the vaccine and (ii) drug product manufacture, which involved formulating, packaging, and storing the vaccine content in preparation for delivery (see **Exhibit 7** for production steps).

The first of several steps in drug substance production was reception and preparation of raw materials, which could include hundreds of different substances varying in availability and handling requirements. In the second step, active ingredient manufacturing, the antigen (i.e., the component that disposed the immune system to fight the pathogen) was produced, typically in a batch process, with relatively large quantities of substances processed in sophisticated vessels called bioreactors. Vessel quality and size were key determinants of productivity, and although usable across different technology platforms, bioreactors, owing to cost to build and capacity constraints, constituted a bottleneck to large-scale production.

To prepare a vaccine from the drug substance produced was also a multi-step process. The first step, coupling and formulation, involved combining the drug substance/antigens with stabilizers, preservatives, and (in the case of mRNA vaccines) with a lipid nano particle. Some vaccines under development also required stabilizers and preservatives to facilitate storage and delivery and adjuvants. Adjuvants enhanced the immune response to the antigen and. Adjuvants helped mitigate the production capacity challenge by requiring less active ingredient per dose as a result of boosting the immune reaction to the antigen. Although often usable across different vaccine candidates, some adjuvants involved rare substances and others were based on complex proprietary technology, posing their own potential bottlenecks to scaling COVID vaccine manufacture.

The glass vials or syringes into which formulated vaccine content was deposited were closed with stoppers and crimped. Some vaccines required additional processes to ensure safety and efficacy through the storage and distribution processes. Fill and finish equipment was costly to build and maintain given the sterility and process control requirements for vaccine products; distribution was complicated by the need for vials and syringes to be labeled and packaged in country-specific formats that signaled adherence to the regulatory requirements for the region or country in which the vaccine was to be used. Packaged vaccine products were released in standardized large lots for cold chain storage and distribution.[14]

Development Platforms and Implications for Manufacturing

The global portfolio of vaccine candidates included a diversity of technology platforms that varied in manufacturing requirements and processes (see **Exhibit 8** for vaccine platforms). Candidates based on well-established technologies like live attenuated would benefit from ample existing manufacturing capacity and considerable institutional experience with production. But the portfolio also included candidates that used novel, untried technologies like DNA and messenger RNA vaccines, never before approved for human use, that, owing to vastly different manufacturing requirements, would likely require entirely new production capacity or costly adjustments to existing facilities.

Live attenuated vaccines boasted nearly 200 years of experience, enjoyed ample existing manufacturing capacity, and were known to provide long-term, highly effective immunity, but development times were long and safety concerns manifold. Protein subunit vaccines (e.g., for flu, HPV, and Hepatitis B) also had a long history of manufacture and were relatively simple to produce in existing facilities, but development time was lengthy and capacity difficult to adjust to an updated version if the initial version proved to have low efficacy. Inactivated vaccines (e.g., for flu, polio, and Hepatitis A) also required lengthy development, regulatory approval, and manufacturing cycle times as well as high levels of biocontainment (i.e., securing facilities against accidental release of pathogens to frontline workers or the population at large), which posed a challenge particularly for green field facilities and capacity building in countries with little regulatory experience in vaccine production (see **Exhibit 9** for projected probability of phase 3 success).

Viral vector vaccines, which used genetically modified versions of other viruses like adenoviruses and pox viruses to induce immunity in humans, could be developed rapidly, but being new and having little existing production capacity, manufacturing scalability was uncertain. Because the viral vector based on a specific virus could be used only once, if an initial vaccine candidate failed, an entirely new vector would need to be created, thus slowing development. Genetic, DNA, and RNA-based vaccines, although not previously licensed for commercial use in humans, were amenable to quick iterations in the lab should initial candidates fail or the pathogen mutate. Their manufacture, requiring much less active ingredient production capacity per dose, could theoretically be rapidly scaled and would be flexible in terms of being able to produce different vaccines in the same category (see **Exhibits 10 and 11** for manufacturing and production targets). The two promising candidates by Pfizer-BioNTech and Moderna, which reported good early results from their Phase III trials in November, used the messenger RNA technology. Genetic vaccines' deep freeze storage and transit (e.g., for messenger RNA vaccines) or advanced delivery devices (e.g., for DNA vaccines) requirement posed potentially significant challenges.

Choice of Production Sites and Economic Geography of Vaccine Manufacturing

Pre-COVID-19, vaccine supply chains allocated production capacity based on cost of manufacturing, volume of domestic and regional demand, and policy incentives. Populous countries such as Brazil, China, and India had invested in building vaccine production capacity domestically to serve local demand (see **Exhibit 12** for vaccine developers by type and location). The complex nature of vaccine production, requiring a well-trained workforce and strong regulatory support, had enabled those countries to build institutional experience and manufacturing capabilities over time, leading them to become regional hubs for vaccine production. Driven by historical experience and cost of production, similar manufacturing clusters had developed in Japan, North America, and South Korea.

Political tensions, such as the pre-pandemic trade war between the US and China, complicated location decisions for COVID-19 vaccine production; in addition, local pressure to reserve initial distribution for domestic populations compromised ample capacity and low production cost in populous developing countries. Serum Institute of India, one of the largest global producers of vaccines and a prominent manufacturer of the promising COVID-19 vaccine candidate developed by AstraZeneca and Oxford University, after reporting pressure from Indian governments to prioritize domestic distribution[15] committed to a 50-50 arrangement whereby half of initial production would be distributed within India and the balance committed to exports.[15]

Nationalist pressure was also exerted on the demand and investment side. Conditioning investment on commitment of large quantities of initial supplies to the US population discouraged some prominent developers and manufacturers from engaging with Operation Warp Speed. The CEO of Serum Institute of India, for example, cited such conditions as the reason for declining an investment by the US Biomedical Advanced Research and Development Authority (BARDA). Several developed nations including Canada and countries in the European Union engaged in similar agreements to secure initial supplies of promising vaccine candidates.

Locating production in developed nations to counter these nationalist tendencies that could restrict vaccine supply would create higher production costs and longer timelines due to the need to add considerable new capacity. Nationalizing vaccine supplies within developed nations also risked international resentment and pernicious political tensions with the developing world.

Situating production in nations with smaller populations, such as Singapore, Hong Kong, and Luxemburg, meant that even after satisfying the requirements of the local population, manufacturers would still be able to distribute large quantities of vaccine throughout the world. Singapore and Hong Kong had

strong economic and trade ties with the rest of the world that could facilitate international coordination and collaboration.

Another consideration related to vaccine production was so-called green (built from scratch) versus brown (existing) site utilization. Often essential for genetic and other novel types of vaccines, green site development tended to be costly and time-consuming, and in countries with little experience in producing and regulating vaccines, posed safety and quality risks. But converting existing brown site facilities could involve a host of pitfalls and was often costly and complex, potentially requiring new machinery, new inputs, different production processes and process designs, as well as additional certifications and approvals from the authorities and vaccine developers.

Financing and Incentives

Building manufacturing capacity for COVID-19 vaccine candidates was costly, and while it was needed to mitigate risk to life and the global economy in the short term, much of that capacity would likely go unused after the crisis abated. Developers were disinclined to invest in it. Advance Market Commitments (AMCs), whereby countries and international initiatives committed to purchase supplies of the most promising vaccine candidates regardless of their success in clinical trials, were a key instrument by which manufacturers were incentivized to build the requisite production capacity. By early November, before any candidates went on the market, governments and international organizations had confirmed purchases of more than 6.4 billion doses of COVID-19 vaccines, and purchases of an additional 3.2 billion doses were under negotiation or reserved as optional expansions to existing deals (see **Exhibit 13** for advance market commitments and procurements by country).

Direct investment and advance purchases by affluent countries risked leaving fewer vaccine supplies for equitable distribution-focused alliances like COVAX. By November 2020, Canada, for example, had committed to purchase enough supplies to vaccinate its population five times over. Less affluent countries with ample existing manufacturing capacity, such as Brazil and India, or with good clinical trial infrastructure, like some other South American countries, were also able to secure vaccine supply deals. Such arrangements risked leaving behind lower income countries without vaccine development capabilities, leaving them reliant on COVAX, which had been negotiating, with little success, with countries that had engaged in individual AMC deals to share some of their supplies with other countries.[16]

Operation Warp Speed contracts, for example, that awarded Pfizer-BioNTech and Moderna USD 1.8 billion and USD 1.5 billion, respectively, required the companies to provide 100 million doses to the US by March 2021 in order to activate large performance bonuses. Pfizer's subsequent announcement that it was expecting to provide the first supplies of 30 to 40 million doses of the promising Pfizer-BioNTech vaccine to the US by the end of the year (Pfizer earnings call, Q3 2020) raised concerns over equitable distribution. Some studies suggested that more than twice the number of COVID-related deaths could be prevented if initial supplies were shared globally rather than distributed within affluent countries.[11]

In fact, Pfizer had not acceded readily to the US public financing scheme, owing to the restrictions it entailed. AMC contracts and public financing had facilitated development of promising COVID-19 vaccine candidates by smaller, unlisted, or recently listed pharma companies with limited resources such as Novavax and Moderna, but the benefits of such arrangements were less clear for larger, publicly-traded pharma companies with vast resources. Pfizer had initially rejected a potential deal on the basis that restrictions on the control of initial supplies would not be worth the USD 0.5 to USD 2 billion in public financing, an amount readily available to the company through the private sector. Only later, after many multinational and smaller pharma companies had accepted public financing/AMC deals with the US and other affluent countries, did Pfizer bow to shareholder pressure and accept a USD 1.8 billion advance

purchase contract with Operation Warp Speed agreeing to provide 100 million doses to the US. In contrast, Moderna, a company that had never taken a vaccine to market, had become a prominent player in the COVID-19 vaccine development race through the large public investment it received.

Raw Material and Component Supply

A further challenge involved procuring in sufficient quantities the ingredients (e.g., lipids) and packaging materials (e.g., vials and syringes), and providing storage adequate for the enormous volume of vaccine that was required. Vaccine manufacturing efforts proved slower through fall 2020 than initially predicted, with several companies, including Pfizer and Moderna, announcing the slower-than-expected vaccine production due to shortages in component and manufacturing equipment supplies.[17] Although ingredient, packaging, and storage requirements were likely to be similar across vaccine candidates, efficiently allocating component supplies across developers and producers would require extensive coordination and collaboration among many parties.

Efficiently allocating scarce component supplies across the global portfolio was seen as key to faster resolution of the COVID-19 crisis. In contrast to BARDA, CEPI, one of the co-leads of the COVAX initiative, had made a large investment to purchase vial supplies from an EU-based manufacturer and committed to equitably allocate those supplies across the initiative's portfolio of developers.[15]

Shortages of packaging and storage materials could be addressed by batching multiple doses of vaccines in individual vials that would be administered to groups of people at the same time and location. This approach would not only conserve valuable glass vial materials and other storage components, but it would also reduce packaging time per dose. Because vaccine components deteriorated quickly (in 24–48 hours), they had to be administered immediately after the seal was broken; therefore, unless sufficient numbers of people were waiting to receive the vaccine, valuable doses could be lost (which was called "vial wastage"). Location-specific demand uncertainty complicated decisions regarding numbers of vials and doses per vial as well as allocations to warehouses and vaccination facilities.

Capacity of bioreactors posed another potential bottleneck. Their production typically entailed lead times of 12 months or more, with the majority of producers based in the developed world. Bioreactor size and quality were key determinants of the productivity of vaccine plants; larger reactors required less floor space per dose, thus conserving capital and minimizing administrative and disposal costs.[18] Single use bioreactors made of specialized polymeric material could be utilized in some cases to mitigate the longer lead times. But the supply of single use bags/bioreactors has also been limited.

Actions being considered to mitigate shortages included:

- global cooperation and coordination to mitigate the effects of nationalized efforts likely to limit the supply for basic components;
- horizontal collaboration across competing developers and manufacturers to optimize allocation of resources (e.g., to ensure that production capacity and packaging materials were allocated to the most effective vaccines as defined by approval);
- speculative manufacturing and pre-approval of manufacturing processes to forestall quality issues subsequent to a vaccine's approval.

Scaling Risks and Scale up versus Scale out

While the companies invested in developing manufacturing capacity in parallel with the clinical trials, mass production proved harder than expected. For example, Pfizer, which had announced it had expected

to produce 100 million doses of the Pfizer/BioNTech vaccine candidate by year's end, later walked back its expected production to about 50 million doses with only half of it allocated to the US.[17] Moderna's output also was disappointing. Several other candidates, including those by Novovax, Johnson & Johnson, and AstraZeneca/Oxford, were based on well-established technologies and, in theory, their manufacture could be scaled up more easily, but the production expectations for these candidates proved overly optimistic as well through fall 2020.

Prior large-scale vaccination programs like those for tuberculosis and polio had targeted specific populations (e.g., children) or geographies, enabling developers and manufacturers to plan and gradually ramp up production. For the COVID-19 vaccine, the manufacturing scale up needed to be achieved much more quickly.

Risk was inherent in scaling up production for vaccine manufacturing. In contrast to vaccines manufactured in small batches for trials, mass production introduced opportunities for greater variability in the quality of raw materials and, hence, greater risk of variation in production quality. The time pressure imposed by the rush to produce a Covid vaccine magnified such risk.

In addition to ensuring a vaccine was safe and effective (known as "design quality"), clinical trials were also necessary to ensure "conformance" or "production" quality—that each dose produced was safe and effective. The phrase "the process is the product" was often used among the industry professionals to describe the importance of process control and design. For many COVID-19 vaccine candidates, production quality and scaling had occurred in parallel with the clinical trials; many subjects in Phase III trials received vaccines produced by large-scale manufacturing processes.

Vaccine volume could be amplified by increasing production in existing facilities, termed "scaling up," or contracting some production to third parties, termed "scaling out." The latter, given the high level of process control required in vaccine production, risked loss of visibility for manufacturing processes, potentially compromising the safety and quality of the product. Scaling out also entailed intellectual property (IP) issues, particularly in countries with track records of IP-theft. Scaling up, however, could incur significant costs and time commitments, especially for companies with little in-house manufacturing experience.

Rushing to meet demand had sometimes resulted in relaxing manufacturing and quality assurance processes and led to poor quality and safety of products which then required doing large scale product recalls. Improper scale-out had tragic consequences for the vaccine developed to treat polio, a disease prevalent in the early 20th century.[19] "The Cutter Incident" referred to more than 200,000 children being infected by a vaccine created by Cutter Laboratories in the mid-1950s. The tragic incident resulted in significant regulatory changes to reduce risk (see **Exhibit 14** for more on the Cutter Incident).

Agile Capacity

Experts predicted a well-funded COVID-19 vaccine candidate to have a 46% chance of reaching Phase III and 16% chance of success from pre-clinical trials to eventual approval. Government and investor grants and advance purchases shielded developers to some degree against the risk of failing trials. But none of these created adequate incentives to plan for potential switchovers—change to new systems—and manufacturing process flexibility. The Serum Institute, for example, had invested USD 300-350 million in land, buildings, and equipment and another USD 100 million or so in ingredients. Much of this investment would have to be written off in the event the AstraZeneca-Oxford vaccine candidate (based on viral vector technology) failed clinical tests, although they could, the CEO reported in an interview, produce another

vaccine that employed similar technology, but would incur switchover costs upwards of USD 100–150 million.

The massive scale of the global effort would require that vaccine manufacturing systems be able to undergo difficult and costly changeovers quickly but safely, and, in the case of genetically-based and other vaccine candidates that employed vastly different technologies, that new capacity be built from scratch. Hence the incentives to encourage developers and manufacturers to build capacity and begin production speculatively for the most promising vaccine candidates at the risk of wasted investment for those that failed to complete clinical trials.

Distribution

Once a vaccine was authorized or licensed for use and went into production, there remained the prodigious challenge of distributing it to a global population of ~7.8 billion people, which included issues related to transportation and delivery of a perishable commodity and ethical considerations that dictated equitable distribution among and within countries.

Equitable International Distribution and Vaccine Nationalism

Despite significant global collaboration early in the crisis, increasing economic and political tensions were luring countries down a "me-first" path. As a result, there had emerged two "camps" around distribution: 1) multilateral cooperation and 2) bilateral agreements between a country and a drug company.

The COVAX Facility led the multilateral cooperation camp;[20] see **Exhibit 15** for participants). A pooled procurement mechanism for vaccine purchases, the COVAX Facility combined participants' buying power and provided volume guarantees to ensure potentially lower prices and provide incentives to vaccine manufacturers (WHO, 2020). In doing this, COVAX aimed to diversify risk across candidates and to assure lower-income countries access to vaccines they would otherwise have been unable to procure. The USD 1.8 billion of the USD 2 billion to be pledged by the end of 2020 (see **Exhibit 16** for fundraising commitments) that COVAX had raised was expected to cover vaccine purchases for developing countries. To distribute the vaccines, the WHO had proposed a "fair allocation" mechanism involving two tiers. The first was based on population size, initial distribution amounting to 3% of the population with additional distribution until 20% of the population was covered. The second tier was based on urgency—speed of spread and the vulnerability of a country's healthcare system.

Doubts about the efficiency of the arrangement and the COVAX Facility's ability to deliver prompted some countries to explore, in parallel, bilateral agreements. France and Germany, for example, remained officially part of COVAX and independently negotiated deals with pharmaceutical companies. Experts including Dr. Clemens Auer, Regional Director of WHO in Europe, expressed concerns about lack of transparency with respect to vaccine selection, price, and quality as well as about COVAX's negotiation of vaccine purchases at a price that included a margin for manufacturers.[21]

Operation Warp Speed, the US' domestic equivalent of COVAX, to which the US Congress had directed USD 10 billion to fund research and development for six vaccine candidates, aimed to manufacture and deliver 300 million vaccine doses.[22]

Uncertainty of vaccine success raised questions about exclusive reliance on domestic vaccine manufacturers.

Equitable Distribution - Domestic Aspects

The US Centers for Disease Control (CDC) announced a phased approach to distribution (see **Exhibit 17** for distribution phases) that would target initially people with high-risk medical conditions, essential workers, healthcare personnel, and adults over 65 years old. On October 2, 2020, the National Academies of Sciences, Engineering, and Medicine released a consensus study recommending to the US Department of Health and Human Services (HHS) and local authorities a four-phased equitable allocation framework (see **Exhibit 18** for framework and population size of each phase).

Willingness to be Vaccinated

Distribution would also have to overcome the challenge of growing skepticism about vaccines. According to an Ipsos survey (see **Exhibit 19** for survey results) of nearly 20,000 adults in 27 countries conducted on behalf of the World Economic Forum in August 2020, only 74% indicated that they would assent to a COVID-19 vaccine. (Scientific opinion held that 70% of the global population would need to be vaccinated to achieve herd immunity.) In the US, for example, nearly half (42.4%) of those polled expressed hesitation about being vaccinated: ~10% indicated that they did not intend to be vaccinated and ~32% that they were uncertain whether they would be (Fisher et al., 2020; see **Exhibit 20** for survey results). Reasons for hesitancy included vaccine-specific concerns, need for additional information, anti-vaccine beliefs, and general lack of trust. Many simply did not want to be among the first to be vaccinated. Nationwide, 75% of Americans indicated that they would be vaccinated given adequate assurance that the vaccine was safe.[23] Distrust taken together with anti-vaccination beliefs, lack of information about vaccines in general and rampant conspiracy theories increased the need for transparency in vaccine development and manufacturing.

Vaccine Transportation Challenges

The challenges posed to vaccine transportation by temperature requirements and the enormous volumes to be shipped were significant. The WHO reported that fully half of all vaccines were wasted globally each year due to temperature control problems as well as logistics and shipment-related issues.[24]

The more than 250 vaccine candidates that had been developed globally as of mid-October 2020 fell into one of two categories regarding temperature requirements for transportation and storage (see **Exhibit 21** for temperature requirements and capacities). The greatest transport capacity was available for the typical pharmaceutical supply chain temperatures of +35–47F (+1-8C). Some of the vaccines under development, however, would have to be transported and stored at sub-zero temperatures of-112F (-80C), for which capacity was much more limited.[25] The Pfizer-BioNTech vaccine candidate, one of the most promising in the portfolio, required this ultracold storage and distribution, which was not supported by most existing cold chain infrastructure and would therefore require costly new freezer capacity for distribution. Moderna's vaccine, another promising candidate, required -20C, supported by most standard freezers. The diversity of requirements of vaccine candidates posed significant challenges in distribution and complicated infrastructure-building efforts.

Proper handling of doses of a given COVID-19 vaccine also required trained personnel and rigorous logistical planning. Many doses would be delivered in large batches including hundreds to thousands of vials, potentially loaded with multiple doses of vaccines. Handling these materials would require good planning to avoid wastage. For example, the Pfizer-BioNTech vaccine would be delivered in insulated boxes including 200 to 1,000 vials, each containing five doses.[26] Once removed from these boxes, the vials had a

shelf life of 5 days in standard refrigeration. The five doses in each vial also had to be used soon after the seal of the vial was broken.

Many less developed countries lacked the infrastructure for cold chain distribution, particularly for ultra-cold chain storage. One study suggested that two-thirds of the world population was unlikely to have ready access to a vaccine that had to be stored at freezing temperatures.[13] The good news, however was that Ebola vaccine, which required cold chain transportation, had been successfully distributed using specialized containers.[26]

Refrigerated warehouse capacity, dispersed globally with a concentration in three countries, China, India, and the US, was in high demand by the food as well as pharmaceutical industries, prompting private companies to construct additional capacity. UPS, for example, announced construction near its air cargo hubs in the US and Germany of dedicated cold storage facilities, each with 600 freezers able to accommodate 48,000 vials of vaccine in insulated boxes of dry ice that would maintain the proper temperature for up to 96 hours. These facilities would, according to UPS, enable overnight delivery to almost any part of the world, employing specialized boxes and temperature monitoring devices on trucks engaged in last-mile delivery. Also, the Internet of Things could provide real-time temperature tracking and analysis.[24]

The volume of shipments posed huge challenges. A COVID-19 vaccine would entail production of approximately 10 billion doses, compared to the existing capacity for producing and distributing 6.4 billion flu vaccine doses per year.[27] According to DHL/McKinsey, to distribute 10 billion vaccine doses would involve ~200,000 movements by pallet shippers on 15,000 flights carrying ~15 million cooling boxes. Large-volume shipments would generate demand spikes for air freight services, as well as for supporting goods including dry ice and glass vials.[13]

Aggressive planning was essential at every step in the supply chain. With billions of vaccine doses needed and the potential for significant losses in cold transit, even seemingly minor operational decisions related to batching and allocating vaccine doses could critically affect distribution and, therefore, lives.

Questions Going Forward

By November 2020, COVID-19 vaccine development saw major advancements in models of scientific collaboration. The search had yielded many promising vaccine candidates, including some developed on new technology platforms. Large public investments in vaccine development and manufacturing capacity incentives—including advance purchases by countries, coupled with companies' willingness to put more capital at risk to build manufacturing plants and produce inventory before approval—had accelerated the speed at which the industry could build sufficient global supplies. But individual vaccine candidates still faced development and manufacturing risks. A portfolio approach to purchasing, as through COVAX, helped diversify risks for vaccine purchasers, but there remained a need for portfolio-level supply network management of capacity and raw material and ancillary supplies and many questions remained:

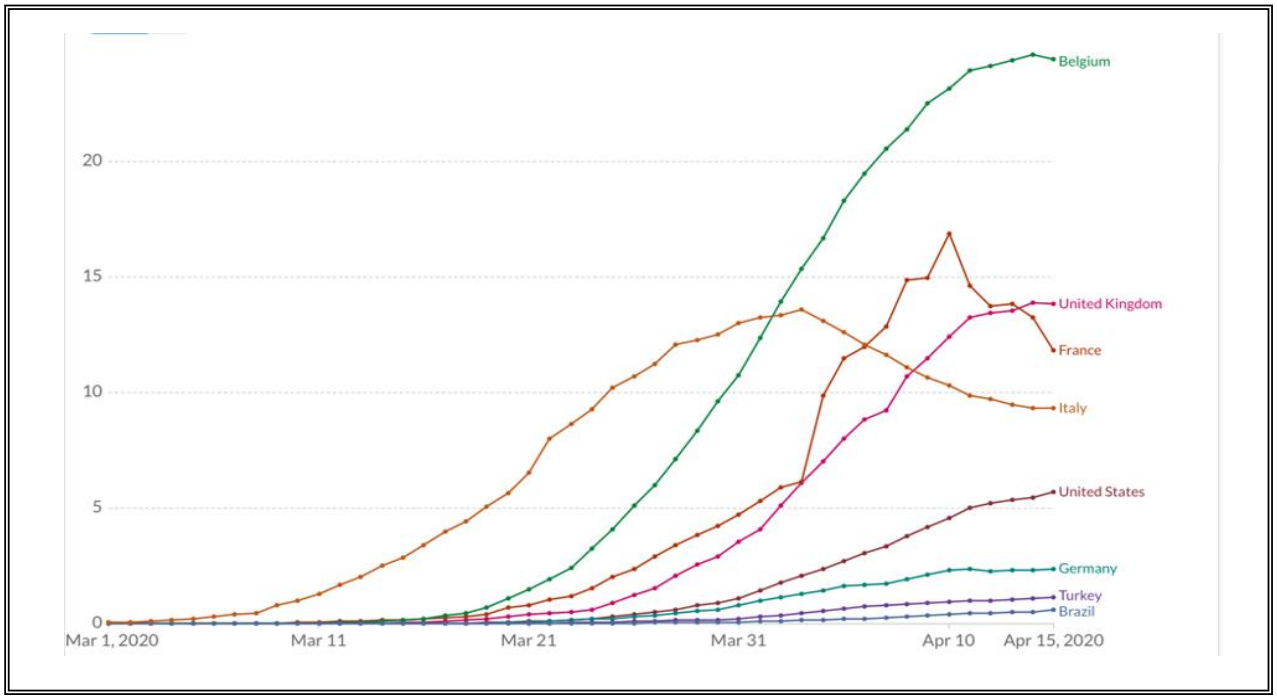
Would voluntary horizontal collaboration between vaccine developers-manufacturers lead to portfolio-level supply coordination? Or should an explicit portfolio-level supply network management function be developed, and, if so, how?

How could the US and other country governments speed up the rate of the vaccine supply chain—from manufacturing to delivery—to counter the risks of variants emerging and the virus mutating?

What were the pros and cons of pre-approval purchase agreements with the US or other national governments, and did the performance clauses in such agreements engender risks that outweighed their

benefit to pharmaceutical companies? How could governments (who were investing in vaccine manufacturing capacity through a combination of grants and advance purchase agreements) ensure sufficient process flexibility in the manufacturing sites so that as information about vaccine efficacy is revealed over time, the manufacturing capacity can be quickly reconfigured? What overall lessons would they take for future pandemics that were becoming more likely as the climate warmed, population grew, and borders were more fluid?

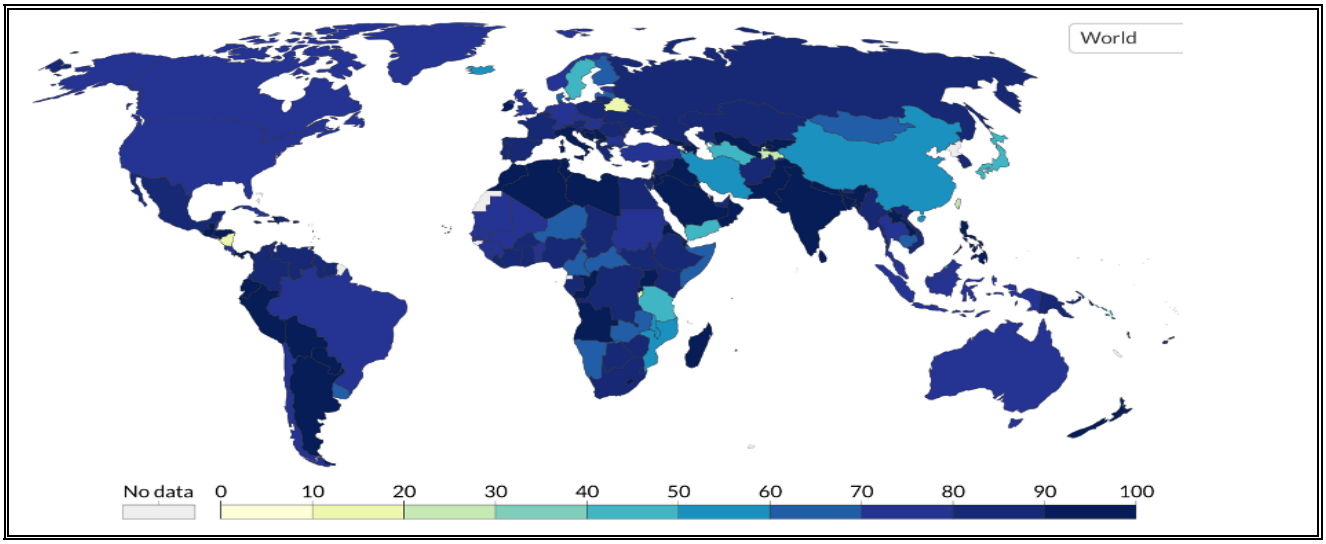
Exhibit 1 *Daily New Confirmed COVID-19 Deaths per Million People**



*7-day rolling average is shown. Limited testing and reporting means that actual numbers may be greater.

Source: Our World in Data, COVID-19 Dataset 2020.

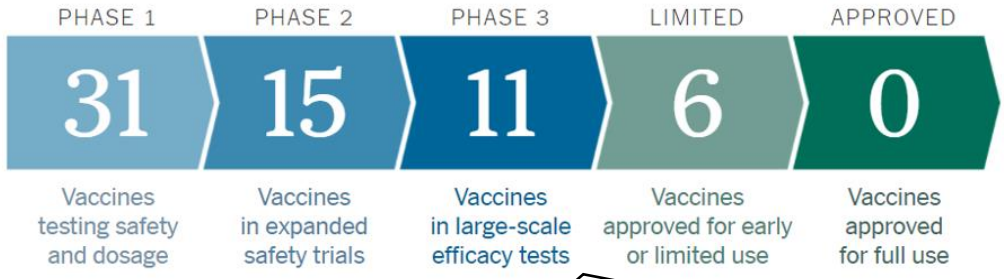
Exhibit 2 *Government Response Stringency Index, April 16, 2020*



Note: This index records the number and strictness of government policies based on nine response indicators calculated from the strictest sub-region's policies, including school closings, workplace closures and travel bans, and should not be interpreted as a score of appropriateness or effectiveness of a country's response.

Source: The Oxford COVID-19 Government Response Tracker 2020.

Exhibit 3 *Coronavirus Vaccine Global Portfolio as of October 16, 2020*



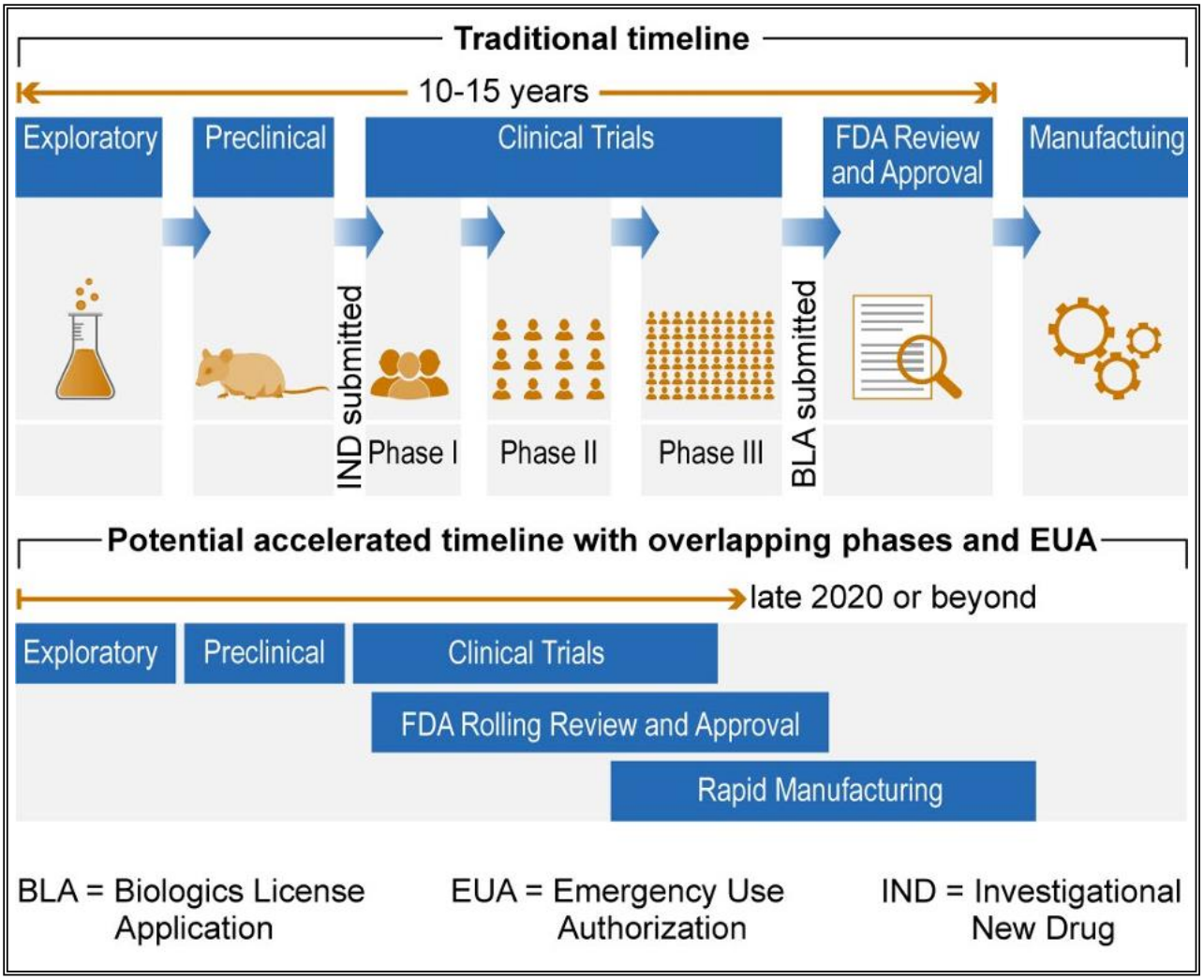
By mid-October 2020, nine likely COVID-19 vaccine candidates for had been identified:

1) Moderna/National Institute of Allergy and Infectious Diseases (US)
2) Pfizer-BioNTech/Fosun Pharmaceutical (US)
3) University of Oxford/AstraZeneca (UK)
4) Sputnik V by the Gamaleya Institute (Russia)
5) Johnson & Johnson's Janssen Pharmaceutical Companies (US)
6) CanSino Biologics/Beijing Institute of Biotechnology (China)
7) Novavax (US)
8) Sinopharm (China)
9) Sinovac Biotech (China)

By mid-November 2020, two vaccine candidates, Pfizer-BioNTech's and Moderna's, had announced early results from Phase III trials indicating that they were highly effective in protecting people against symptomatic COVID-19 infection.

Sources: Corum, Wee, & Zimmer, 2020; Le, Cramer, Chen, and Mayhew, 2020; Loftus et al, 2020.

Exhibit 4 *Vaccine Development Process*



Source: GAO analysis of GAO-20-215SP, FDA, HHS, and Pharmaceutical Research and Manufacturers of America (PhRMA) documentation. GEO-20-583SP.

Exhibit 5 *Historical and Expert Projections of Time Needed to Complete Each Phase of Vaccine Development*

Item	Preclinical	Phase 1	Phase 2	Phase 3	Approval
*Historical vaccine development (**years**)*					
Simple vaccine	3.3	1.6	2.2	2.3	Not available
Complex vaccine	3.3	2	3.7	3.7	Not available
*Expert's forecast for COVID-19 vaccine development (**months**)*					
Most likely scenario	3	2	3	3	1
20th percentile	6	4	5	9	3
80th percentile	12	6	8	18	6

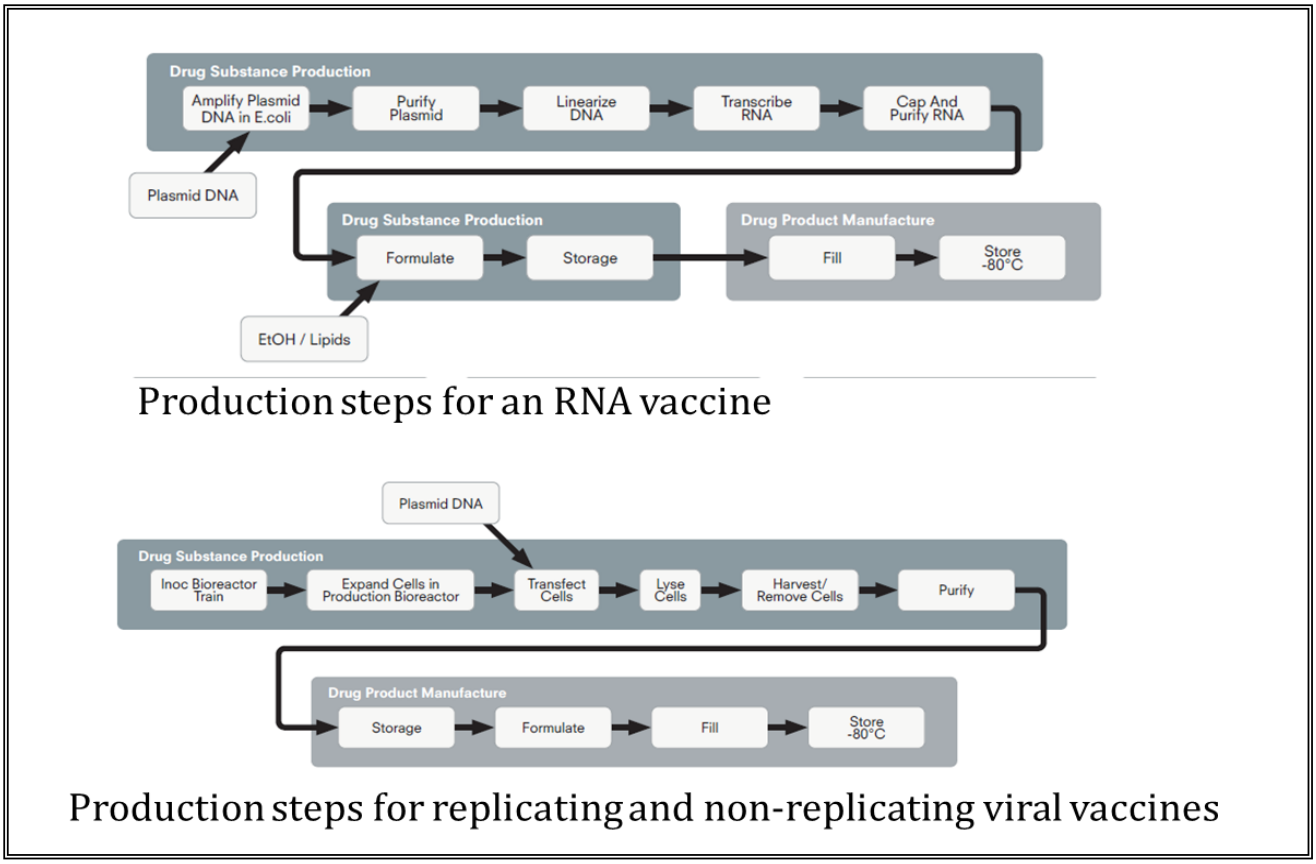
Source: McDonnell et al., 2020

Exhibit 6 *Factors Causing Variability in Biopharmaceutical Manufacturing and Implications for Vaccine Production*

Cause of variability	Description	Implication
Molecule or virus complexity	2,500–25,000 atoms in protein-based vaccines; even greater complexity in virus-based vaccines	High-value product
Molecule or virus stability	Great sensitivity to heat, pH, and organic solvents	Relatively short shelf life (18–36 months)
Production principle	• Recombinant technology, typically with >15 steps • Sterile design for drug substance and drug product	Complicated and expensive production requirements
Scalability	Difficult, up to approximately 20,000 liters	Limited output per production line
Cell banking	• Sterile handling • Master cell banks maintained at, eg, –120°C	Complicated process
Raw materials	Typically >50 raw materials with many critical specs (eg, residual heavy metals)	Heavy test load on raw materials; difficult quality control
Purification	Multistep chromatography	Expensive step with high-cost consumables
Lead time to drug substance	Weeks to months	Long lead time
Storage	Cold room (2–8°C) and frozen	Tight supply chain control required
Transport	Cold chain transport in frozen state for drug substance and at 2–8°C for drug product	Tight transport control required

Source: McKinsey, 2020.

Exhibit 7 *Production of Drug Substance and Manufacture of Drug Product for mRNA and Viral Vector Vaccines*



Source: McDonnell et al., 2020

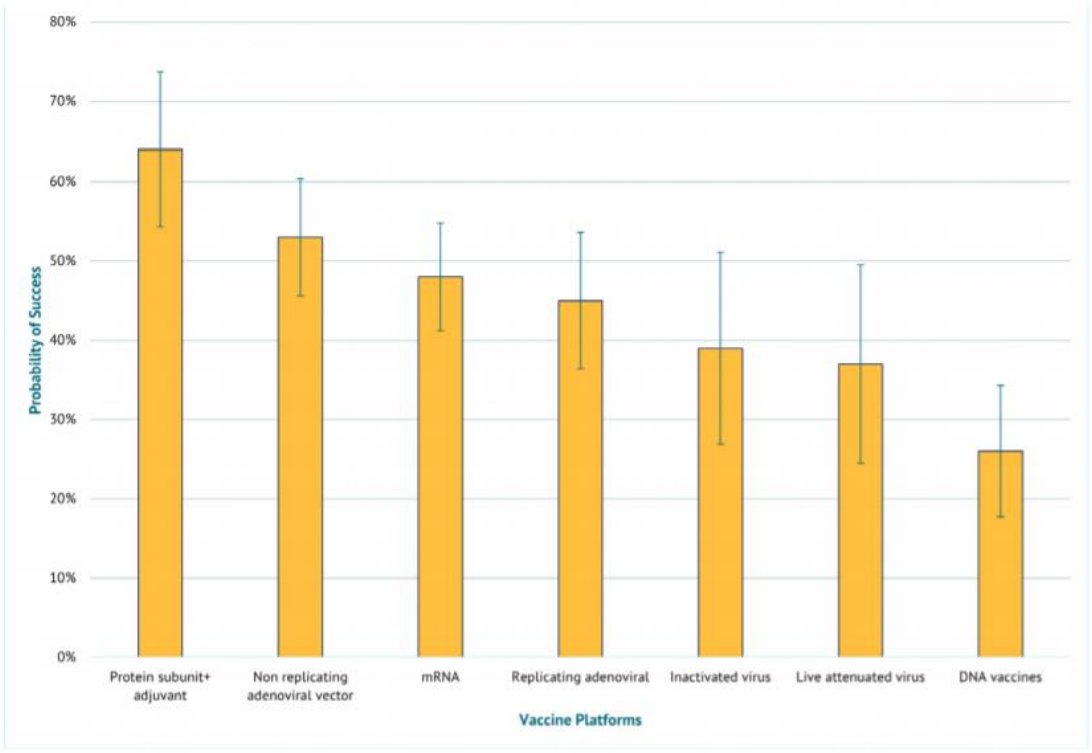
Exhibit 8 *COVID-19 Vaccine Platforms*

Platform	Novel?	Number of candidates	Percentage of portfolio	Examples	Experts who indicated faster	Experts who indicated slower	Our aggregations (model input)
Protein subunit	No	92	39.1	Flu vaccine	2 faster, 1 fastest	2 slightly slower, 1 slower	Standard timing
RNA	Yes	30	12.8		1 faster, fastest	1 slower	Slightly faster (90% of standard timing)
Non-replicating viral vector	No	29	12.3	Ebola vaccine	1 faster	2 slower	Slightly slower (110% of standard timing)
DNA	Yes	20	8.5		1 faster	1 slower, 1 very slow	Slower (133% of standard timing)
Replicating viral vector	Yes	20	8.5		None	2 slower	Slower (133% of standard timing)
Inactivated	No	14	6	Polio vaccine	2 faster one "second fastest"	1 slower	Faster (75% of standard timing)
Other	No	6	2.6		None	3 slower, 3 very slow	Much slower (twice standard timing)
Live attenuated	No	4	1.7	Childhood vaccines for measles, mumps, and rubella (MMR)	1 faster	3 said slower, another 3 said much slower	Much slower (twice standard timing)
Unknown	No	20	8.5				

Note: Vaccines for which we could not determine the platform were not included in the analysis.

Source: McDonnell, et al. 2020 and case writers.

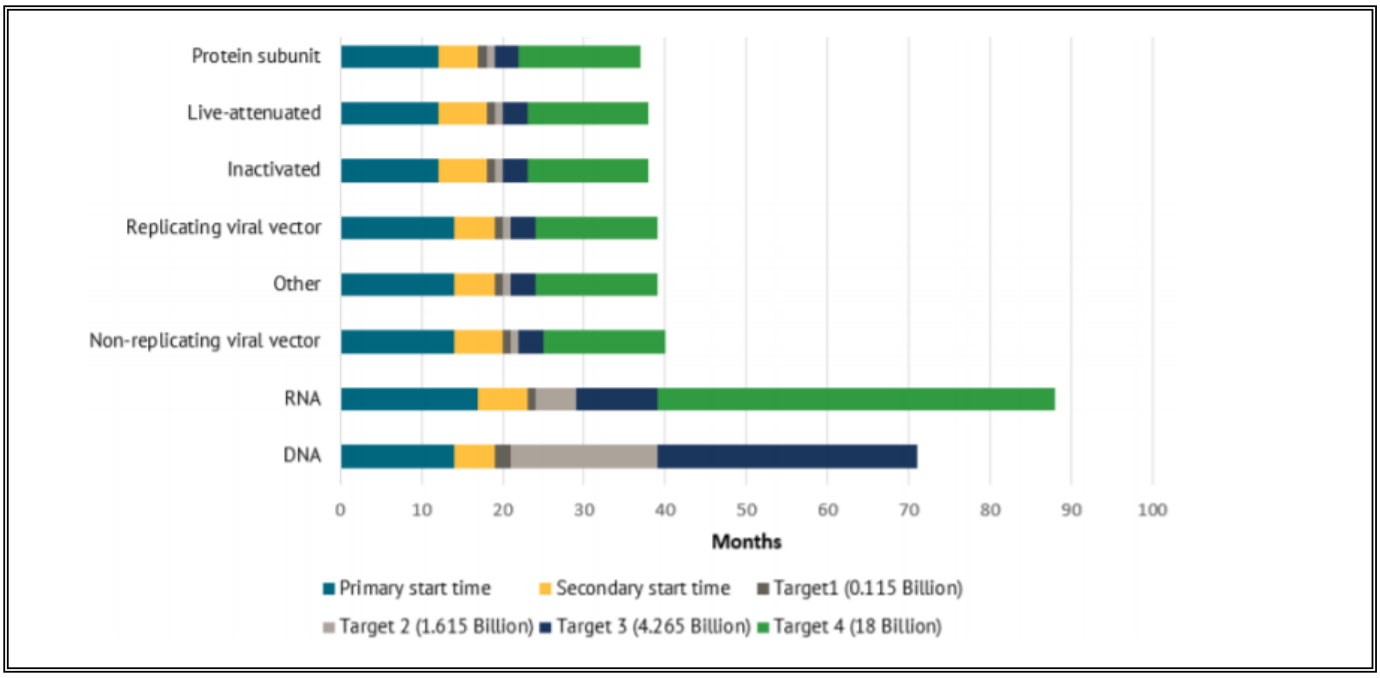
Exhibit 9 *Projected Probability of Success of a Phase 3 Trial of the Seven Platforms for COVID-19 Vaccine, According to Interviewed Experts*



Note: Yellow bars show mean values. Blue lines show 95% confidence intervals

Source: McDonnell et al., 2020.

Exhibit 10 *Time to Manufacture Enough Vaccine to Meet Targets, by Platform*

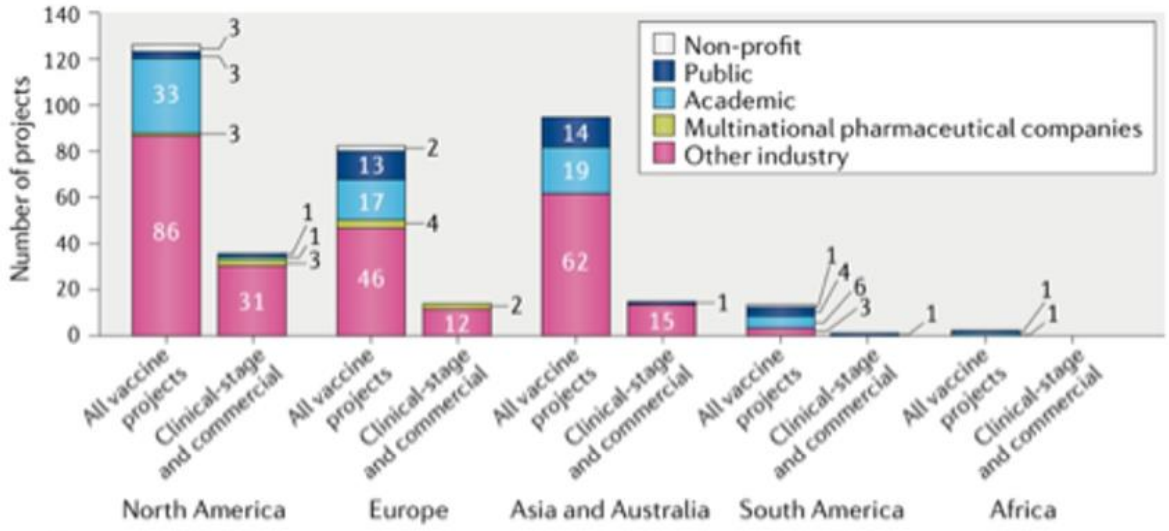


Source: McDonnell et al., 2020.

Exhibit 11 *Projected Production of Vaccines by Platform and Target Group*

Source: McDonnell et al., 2020.

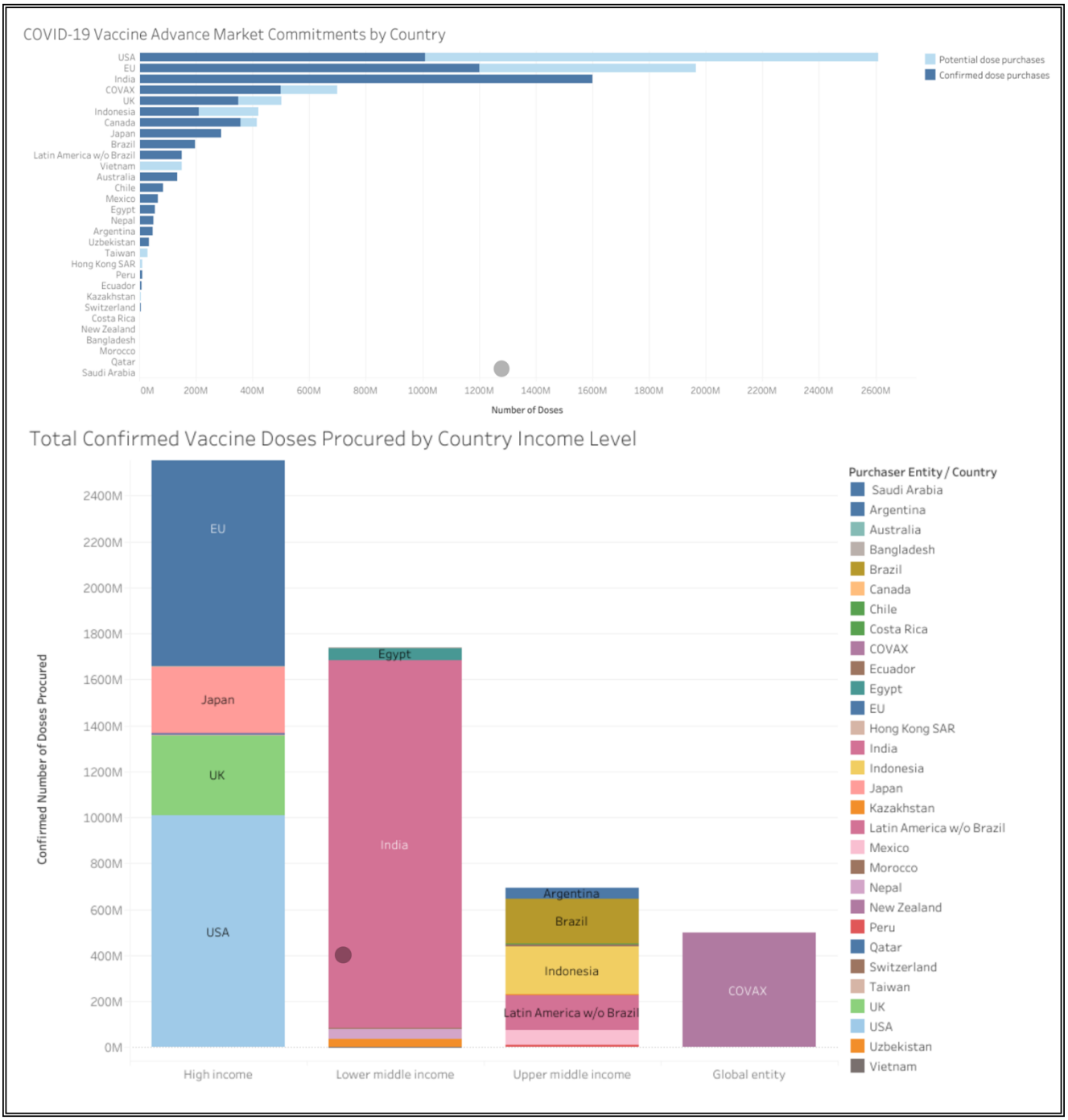
Exhibit 12 *Profile of COVID-19 Vaccine Developers by Type and Geographic Location*



Note: "Multinational pharmaceutical companies" are defined as having revenues of more than USD 10 billion per year. "Other industry" includes smaller companies. Locations represent that of the lead developer.

Source: McDonnell et al., 2020.

Exhibit 13 *COVID-19 Vaccine Advance Market Commitments by Country*



Source: Duke Global Health.

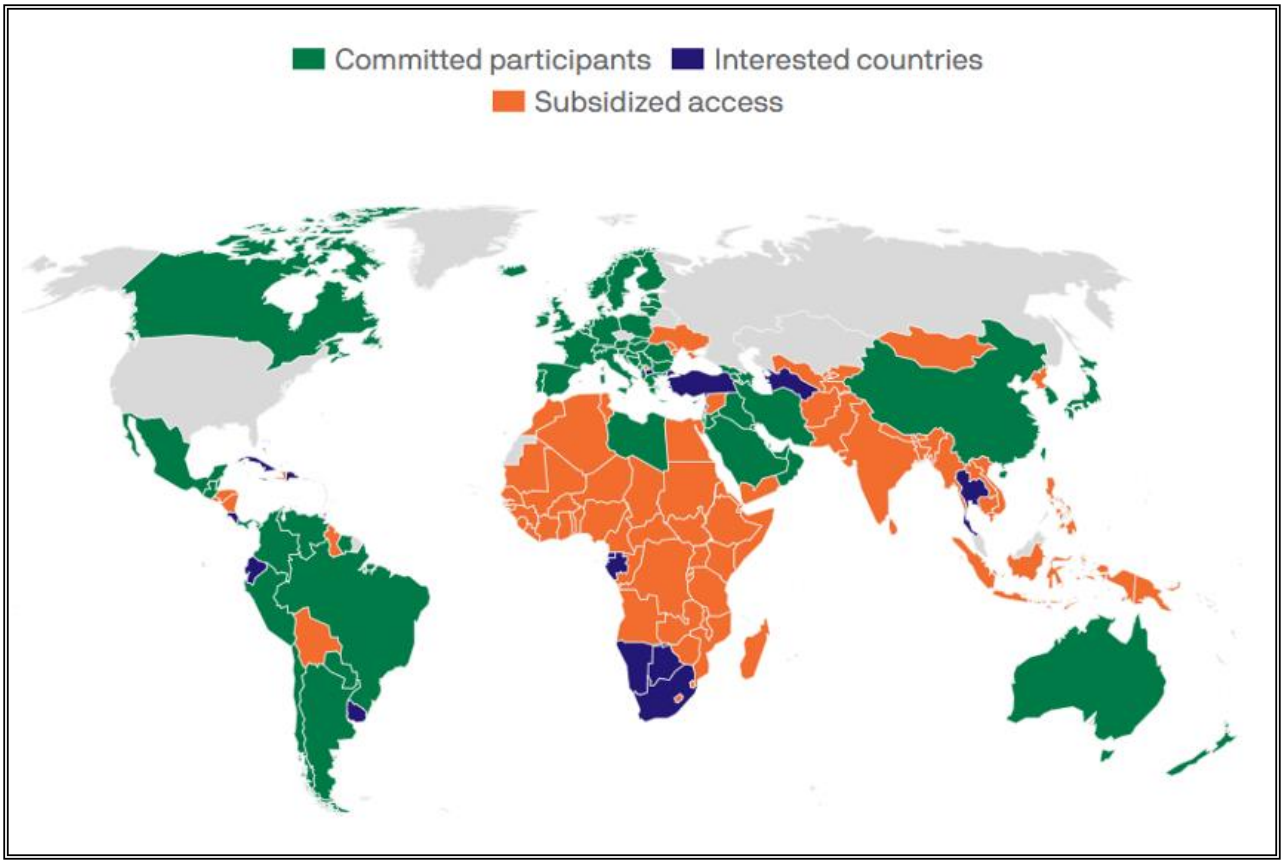
Exhibit 14 *The Cutter Incident*

Summer spikes in polio cases during the 1940s had resulted in some 35,000 people becoming paralyzed and hundreds dying annually. There being no treatment for polio, a vaccine had been sought. Following medical trials that demonstrated 80%-90% efficacy, the Salk vaccine was approved in 1955. Production ramped up quickly and by April 1955 more than 200,000 children in five Western and Mid-Western US states had received the immunization. Reports of polio symptoms had surfaced within days. Investigations revealed the vaccine to have caused 40,000 cases of polio leaving 200 children paralyzed and 10 dead. The responsible vaccine had been produced from a live polio virus by Cutter Laboratories. Several factors contributed to this problem. A different process was used for large-scale manufacturing than had been used to produce the small batches for the clinical trials. The virus was killed through treatment with formaldehyde for some length of time, but the initial estimates of how long to treat for the large-scale manufacturing process proved too low. Finally, quality was at the batch, not process level. For example, if 12 batches were produced and 6 were found to be defective (i.e., the virus was still alive), that should have been taken as indicative of a faulty process and a root cause analysis should have been conducted, which would have revealed that a longer formaldehyde treatment time was needed. Instead, Cutter Laboratories simply threw away the defective batches and shipped the rest. Given that quality testing is imperfect, some of those shipped batches were later found to still have live virus and that's what caused the polio outbreak.

The "Cutter Incident" resulted in regulatory changes that reduced risk for new vaccines. A biological research division, which subsequently became the Center for Biological Research and Evaluation, part of the US Food and Drug Administration (FDA), was established by the National Institutes of Health (NIH) in June 1955. The FDA strengthened vaccine manufacturing requirements including processes for filtration, storage, and safety testing and published manufacturing regulations for drugs and biologicals, which included, for example, standards for materials, cleanliness, security, record keeping, quality events, and staff certification. There are now sufficient quality safeguards in place in modern day vaccine manufacturing to prevent manufacturing disasters like the "Cutter Incident," with each step in vaccine manufacturing requiring very meticulous quality control steps which constitute up to 50% of the manufacturing lead-time. Attempts to speed up production had to ensure that they would not circumvent or compromise any of the quality assurance steps.

Source: Fitzpatrick M. (2006).

Exhibit 15 *COVAX Vaccine Initiative Participants*



Source: Gavi, The Vaccine Alliance; Map: Naema Ahmed/Axios.

Exhibit 16 *Key Outcomes of COVAX Fundraising*

US$ million[1]

Commitments to Gavi

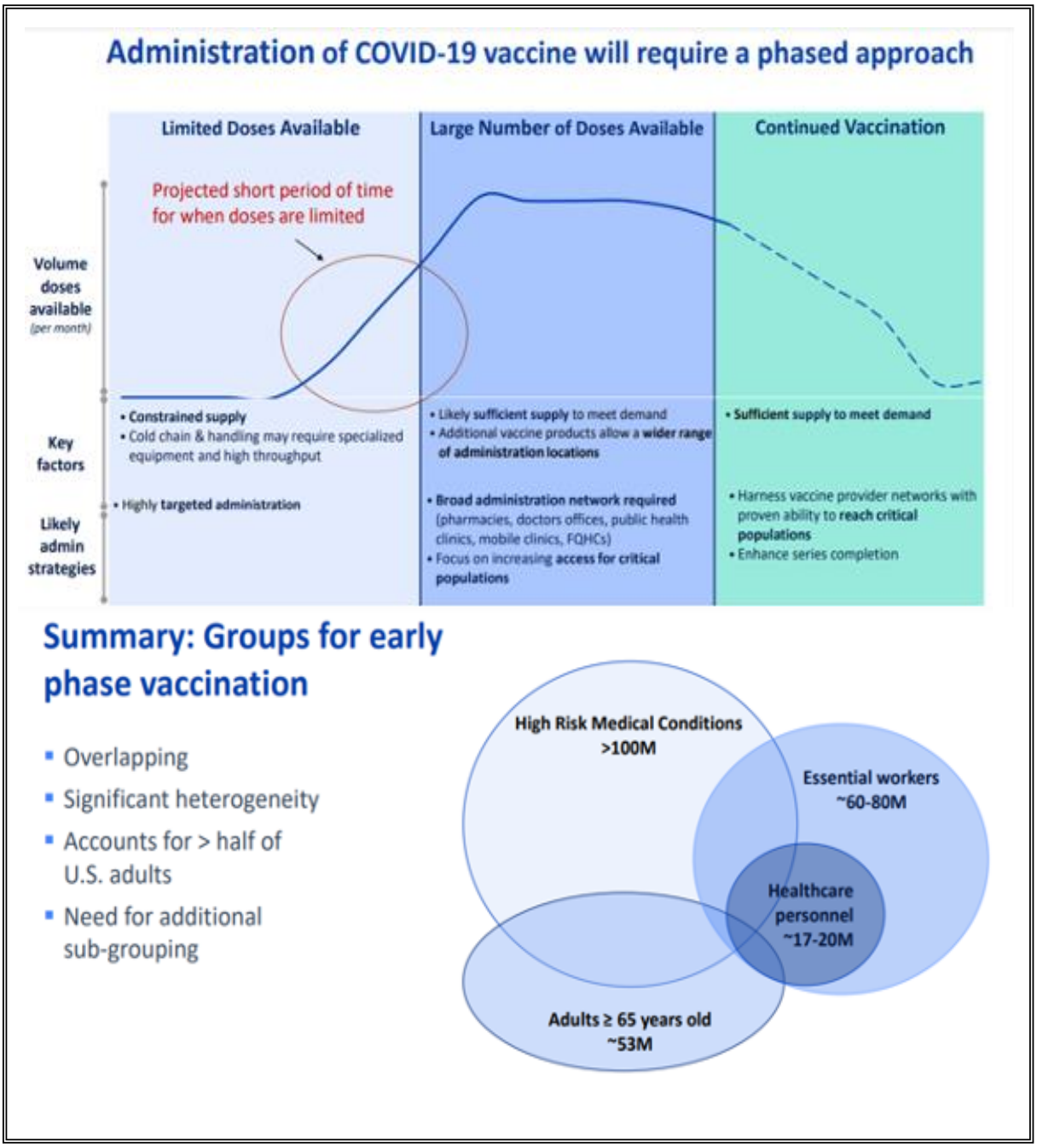
	Note	Curr.	Contribution (LC)	FX rate	Contribution USD	Resources now Assured
Donor Governments						
Australia		AUD	80.0	0.7400	59.2	59
Bhutan		USD	0.005	1.0000	0.005	0.005
Canada	2	USD	194.4	1.0000	194.4	194
Colombia		USD	0.5	1.0000	0.5	1
Germany		EUR	100.00	1.2000	120.0	120
Greece		EUR	1.50	1.2000	1.8	2
Iceland		ISK	250.0	0.0073	1.8	2
Italy	3	USD	103.4	1.0000	103.4	103
Japan		USD	130.0	1.0000	130.0	130
Kuwait		USD	10.0	1.0000	10.0	10
Monaco		EUR	0.05	1.2000	0.1	0.1
Netherlands		EUR	5.00	1.2000	6.0	6
New Zealand		NZD	7.0	0.6800	4.8	5
Norway	4	USD	25.9	1.0000	25.9	26
Qatar		USD	10.00	1.0000	10.0	10
Saudi Arabia		USD	153.0	1.0000	153.0	153
Switzerland		CHF	20.0	1.1100	22.2	22
Sweden		SEK	100.0	0.1160	11.6	12
United Kingdom	5, 6	USD	730.6	1.0000	730.6	731
Foundations, Corporations and Organisations						
Anonymous Foundation		CHF	20.00	1.1100	22.2	22
Bill & Melinda Gates Foundation (BMGF)	7	USD	106.25	1.0000	106.3	106
Gamers Without Borders		USD	1.30	1.0000	1.3	1
Mastercard		GBP	1.00	1.3400	1.3	1
Reed Hastings and Patty Quillin		USD	30.00	1.0000	30.0	30
TikTok	8	USD	10.00	1.0000	10.0	10
Transferwise		USD	7.00	1.0000	7.0	7
Soccer Aid		GBP	3.00	1.3400	4.0	4
Total Pledged to date					1,767	1,767
						$1.8 bn
Guarantees						
Team Europe (European Commission/EIB)	9	EUR	400.00	1.2000	480	

Notes

1 Fx Rates established as of August 31, 2020 in line with v.18 of Gavi's Financial Forecast
2 Represents US$ 25m of pro-rata share of un-allocated AMC-PCV funds
3 Represents US$ 79.4m of pro-rata share of un-allocated AMC-PCV funds
4 Represents US$ 6.3m of pro-rata share of un-allocated AMC-PCV funds
5 Represents US$ 60.6m of pro-rata share of un-allocated AMC-PCV funds
6 Including GBP 250m contingent on others joining COVAX AMC
7 Includes US$ 6.3m of pro-rata share of un-allocated AMC-PCV funds
8 Includes BMGF matching funds of US$ 5m
9 As part of Team Europe, towards purchasing future vaccines to the benefit of low and middle income countries

Source: Gavi, The Vaccine Alliance.

Exhibit 17 *CDC Approach to Early Vaccine Distribution in the US*



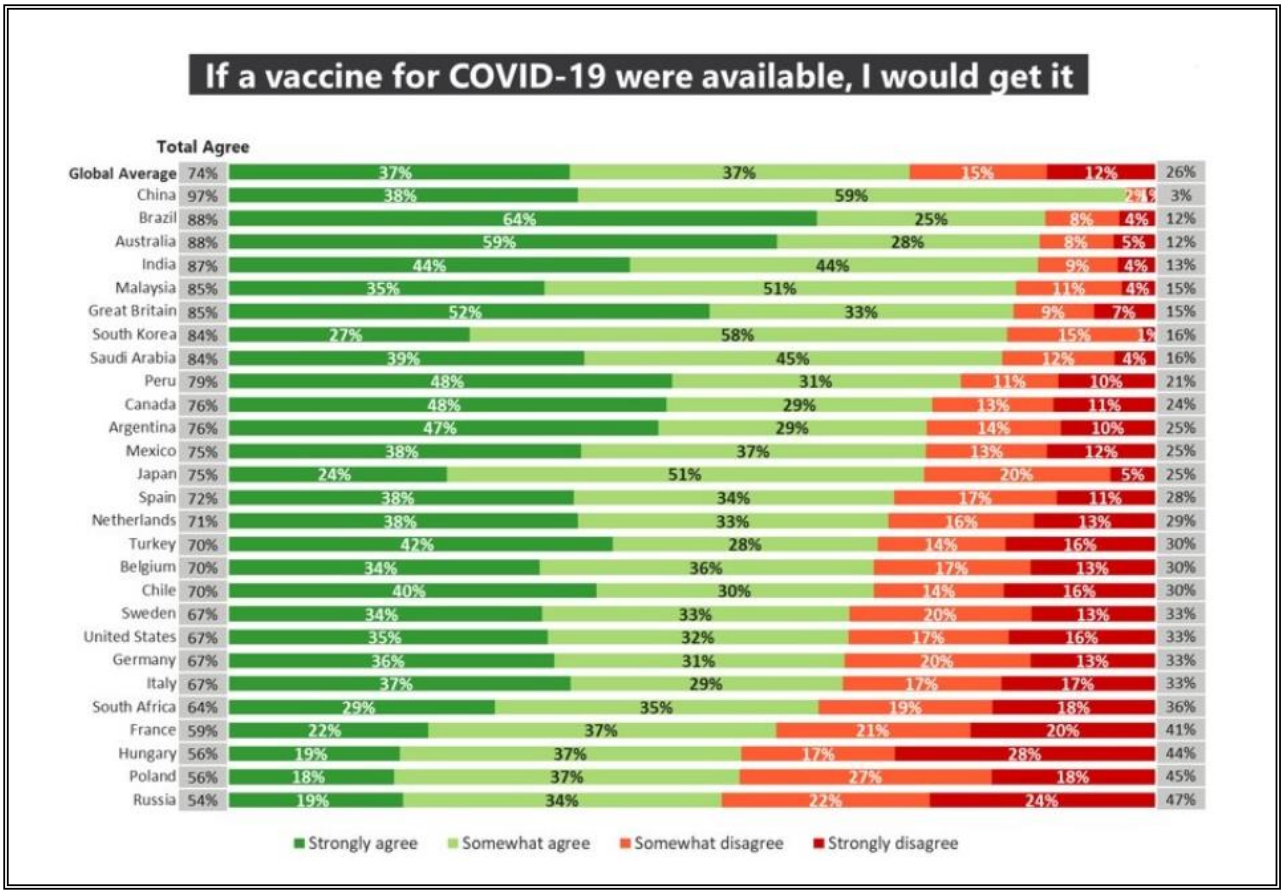
Source: Dooling, 2020.

Exhibit 18 *The National Academies of Sciences, Engineering, and Medicine Framework for Equitable Allocation of COVID-19 Vaccine Recommendations and Size of Each Phase*

Phase 1	Phase 2	Phase 3	Phase 4
Phase 1a ("Jumpstart Phase") ♦ High-risk health workers ♦ First responders Phase 1b ♦ People of all ages with comorbid and underlying conditions that put them at significantly higher risk ♦ Older adults living in congregate or overcrowded settings	♦ K-12 teachers and school staff and childcare workers ♦ Critical workers in high-risk settings – working who are in industries essential to the functioning of society and at substantially higher risk of exposure ♦ People of all ages with comorbid and underlying conditions that put them at moderately higher risk ♦ People in homeless shelters or group homes for individuals with disabilities, including serious mental illness, developmental and intellectual disabilities, and physical disabilities or in recovery and staff who work in such settings ♦ People in prisons, jails, detention centers, and similar facilities and staff who work in such settings ♦ All older adults not included in Phase 1	♦ Young adults ♦ Children ♦ Workers in industries and occupations important to the functioning of society and at increased risk of exposure not included in Phase 1 or 2	♦ Everyone residing in the US who did not have access to the vaccine in previous phases
Equity is a crosscutting consideration: In each population group, vaccine access should be prioritized for geographic areas identified through CDC's Social Vulnerability Index or another more specific index			
1a) 5% of the population 1b) 10% of the population (people with underlying high risk medical conditions)	25-30% of the population (school and childcare workers)	40–45% of the population (young adults and high-risk workers)	Everyone else

Sources: NASEM, Framework for Equitable Allocation of COVID-19 Vaccine 2020 and case writers.

Exhibit 19 *Ipsos Global Survey Results*



Source: IPSOS 2020.

Exhibit 20 *Attitudes Toward a Potential SARS-CoV-2 Vaccine: A Survey of US Adults*

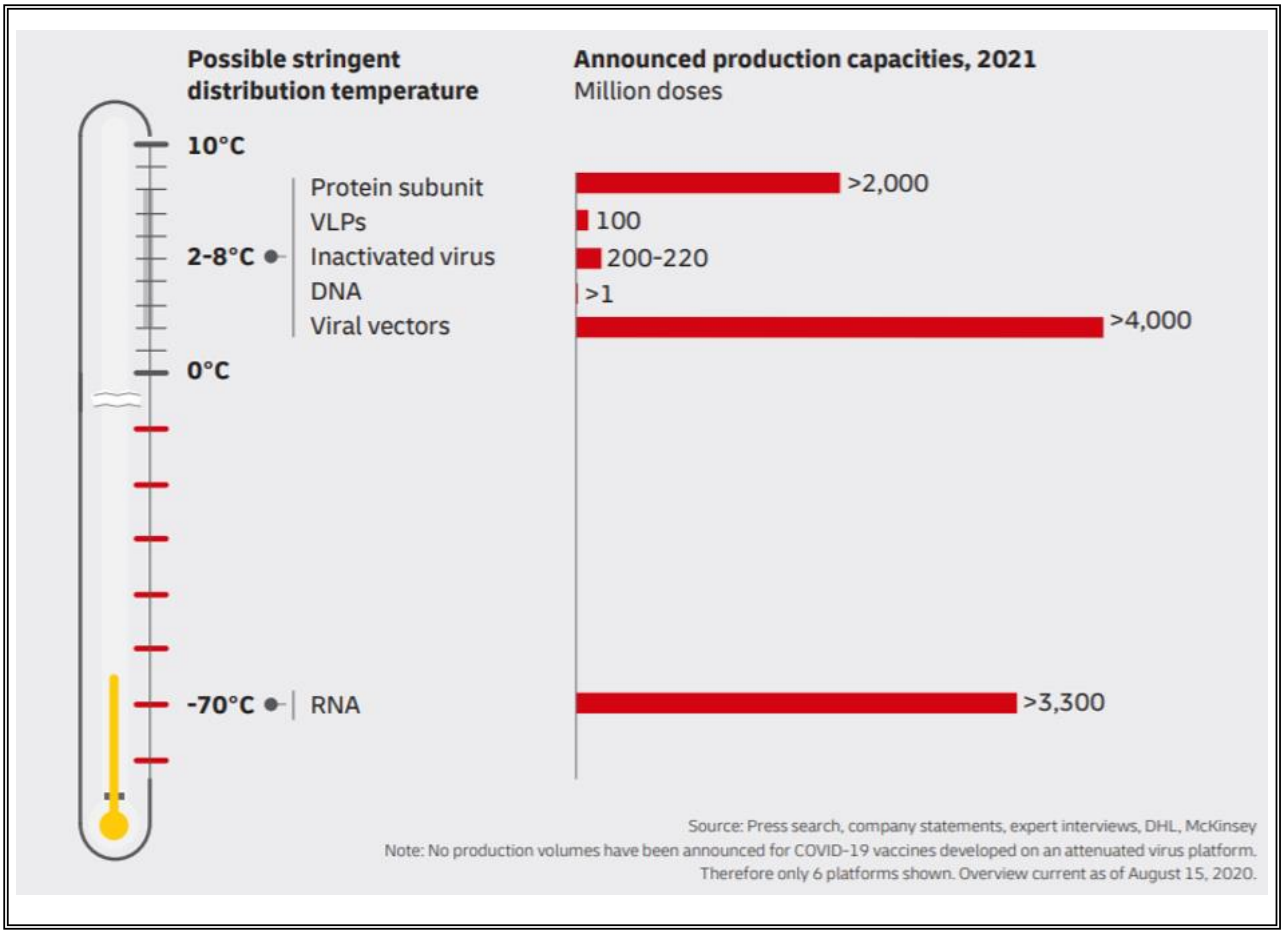
Table 2. Intent to Be Vaccinated, by Participant Characteristics

Characteristic	Intent to Be Vaccinated, *n* (%)			*P* Value	
	Yes (*n* = 571)	Not Sure (*n* = 313)	No (*n* = 107)	Yes vs. Not Sure	Yes vs. No
Age group				<0.001	<0.001
18-29 y	100 (49.6)	82 (40.5)	20 (9.9)		
30-44 y	116 (47.0)	91 (36.8)	40 (16.2)		
45-59 y	127 (52.0)	88 (35.9)	29 (12.1)		
≥60 y	228 (76.5)	53 (17.7)	17 (5.8)		
Gender				0.002	0.035
Female	263 (51.6)	186 (36.4)	61 (12.0)		
Male	308 (64.0)	128 (26.5)	46 (9.5)		
Race/ethnicity				<0.001	<0.001
Asian, non-Hispanic	27 (77.5)	7 (22.5)	0 (0.0)		
Black, non-Hispanic	47 (39.3)	48 (40.5)	24 (20.2)		
Hispanic	72 (44.5)	66 (40.7)	24 (14.8)		
Other, non-Hispanic	11 (57.2)	4 (19.6)	5 (23.3)		
Two or more races, non-Hispanic	16 (55.5)	10 (34.1)	3 (10.5)		
White, non-Hispanic	398 (63.5)	178 (28.3)	51 (8.2)		
Educational attainment				<0.001	<0.001
No high school diploma	45 (46.6)	31 (32.2)	20 (21.2)		
High school graduate or equivalent	129 (46.2)	113 (40.6)	37 (13.3)		
Some college	155 (56.5)	84 (30.7)	35 (12.8)		
College graduate or above	242 (70.9)	85 (24.9)	14 (4.2)		
Annual household income				0.002	<0.001
<$30 000	131 (49.4)	91 (34.3)	43 (16.3)		
$30 000 to <$60 000	147 (52.9)	99 (35.5)	32 (11.6)		
$60 000 to <$100 000	143 (60.0)	73 (30.7)	22 (9.3)		
≥$100 000	150 (71.1)	50 (24.1)	9 (4.3)		
Household size				0.002	0.024
1	99 (64.6)	37 (24.3)	17 (11.1)		
2	197 (64.6)	85 (27.9)	23 (7.6)		
3	74 (52.3)	51 (36.1)	16 (11.6)		
4	73 (58.4)	39 (31.4)	13 (10.2)		
5	43 (56.4)	24 (31.7)	9 (11.9)		
6	84 (44.7)	76 (40.3)	28 (15.1)		
Geographic location, census region				0.003	0.52
Northeast	115 (66.5)	43 (24.8)	15 (8.8)		
Midwest	129 (62.4)	53 (25.7)	24 (11.9)		
South	197 (51.9)	140 (37.1)	42 (11.0)		
West	130 (55.9)	77 (33.1)	25 (11.0)		
Setting				0.62	0.001
Urban	502 (58.5)	279 (32.5)	77 (9.0)		
Rural	69 (51.9)	34 (25.8)	29 (22.3)		
Have you had either a flu shot or flu spray in the nose within the past year?†				<0.001	<0.001
Yes	406 (77.7)	103 (19.7)	13 (2.6)		
No	165 (35.3)	210 (44.9)	92 (19.8)		
What is your best guess as to whether you will get the coronavirus within the next 6 months?‡				<0.001	0.076
I don't think I will get the coronavirus	327 (52.6)	227 (36.5)	68 (10.9)		
I think I will get a mild case of the coronavirus	173 (65.6)	64 (24.4)	26 (10.0)		
I think I will get seriously ill from the coronavirus	44 (75.4)	9 (16.3)	5 (8.3)		
I have already had the coronavirus	16 (58.1)	4 (15.4)	7 (26.6)		
Self-rated overall health†				0.047	0.64
Excellent/very good	288 (60.8)	137 (28.9)	48 (10.3)		
Good	194 (52.8)	133 (36.1)	41 (11.1)		
Fair/poor	89 (59.5)	44 (29.3)	17 (11.2)		

* Percentages may not total to 100 owing to rounding.
† Missing data from <1% of participants (n = 1 in "no" column).
‡ Missing data from <2.5% of participants (n = 13 in "yes" column, n = 9 in "not sure" column, and n = 1 in "no" column).

Source: Fisher et al. 2020

Exhibit 21 *Announced Production Capacities and Possible Distribution Temperatures*



Source: McKinsey/DHL 2020.

References

1. Leadership Live with David Rubenstein, https://www.bloomberg.com/qt/series/leadership-live (accessed 9 July 2021).
2. Interview with Dr. Nicholas Christakis. *PBS News Hour*, https://www.pbs.org/newshour/show/even-with-a-vaccine-covid-19-will-last-for-years-expert-says (2020).
3. Weintraub RL, Subramanian L, Karlage A, et al. COVID-19 Vaccine To Vaccination: Why Leaders Must Invest In Delivery Strategies Now. *Health Affairs* 2020; 40: 33–41.
4. Serdobova I, Kieny MP. Assembling a global vaccine development pipeline for infectious diseases in the developing world. *American journal of public health* 2006; 96: 1554–1559.
5. McDonnell A, Van Exan R, Lloyd S, et al. COVID-19 Vaccine Predictions: Using Mathematical Modelling and Expert Opinions to Estimate Timelines and Probabilities of Success of COVID-19 Vaccines. *Center For Global Development*, https://www.cgdev.org/publication/covid-19-vaccine-predictions (accessed 14 December 2020).
6. Phelan AL, Eccleston-Turner M, Rourke M, et al. Legal agreements: Barriers and enablers to global equitable COVID-19 vaccine access. *The Lancet* 2020; 396: 800–802.
7. Lee J. There are seven coronavirus vaccine candidates being tested in the U.S, https://www.marketwatch.com/story/there-are-seven-coronavirus-vaccine-candidates-being-tested-in-the-us-heres-where-they-stand-2020-09-08 (2020).
8. Ensuring the Safety of Vaccines in the United States, https://www.cdc.gov/vaccines/hcp/conversations/ensuring-safe-vaccines.html (2018).
9. Corum J, Wee S, Zimmer C. , https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html (2020).
10. Fisher KA, Bloomstone SJ, Walder J, et al. Attitudes Toward a Potential SARS-CoV-2 Vaccine: A Survey of U.S. *Adults Annals of Internal Medicine*. Epub ahead of print 2020. DOI: 10.7326/m20-3569.
11. D'Urbino L. The promise of the new COVID-19 vaccine is immense. *The Economist*, https://www.economist.com/leaders/2020/11/14/the-promise-of-the-new-covid-19-vaccine-is-immense (2020).
12. Cottrill K. Researchers offer logistics fix to flu outbreaks, https://news.mit.edu/2005/flu (2005).
13. Resilience DP. DHL/McKinsey, https://www.dhl.com/content/dam/dhl/global/core/documents/pdf/glo-core-delivering-pandemic-resilience-2020.pdf (2020).
14. How are vaccines produced?, https://www.vaccineseurope.eu/about-vaccines/how-are-vaccines-produced (2020).
15. The Documentary Podcast - Vaccines, money and politics - BBC Sounds, https://www.bbc.co.uk/sounds/play/p08nblh3 (2020).
16. Health DG. , https://launchandscalefaster.org/COVID-19 (2020).

17. Thomas K. The Vaccines Will Probably Work. Making Them Fast Will Be the Hard Part. *New York Times*, https://www.nytimes.com/2020/11/17/health/coronavirus-vaccine-operation-warp-speed.html (2020).

18. Arthur R. Serum Institute to double COVID-19 vaccine productivity with ABEC's bioreactors, https://www.biopharma-reporter.com/Article/2020/09/30/Serum-Institute-to-double-COVID-19-vaccine-productivity-with-ABEC-s-large-bioreactors (2020).

19. Offit PA. The Cutter Incident: How America's First Polio Vaccine Led to the Growing Vaccine Crisis.

20. Lawler D. Vaccine initiative now covers almost entire world, but not U.S. or Russia, https://www.axios.com/covax-initiative-vaccines-china-joins-trump-russia-26dce1f3-1b81-47af-8b7d-199900a928f3.html (2020).

21. Hinnant L, Cheng M. Push to Bring Vaccines to Poor Faces Trouble, https://www.designdevelopmenttoday.com/industries/medical/news/21196223/push-to-bring-vaccines-to-poor-faces-trouble (2020).

22. Fact Sheet: Explaining Operation Warp Speed, https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html (November 13).

23. Bernstein S. Most Americans would take coronavirus vaccine if deemed safe: Reuters/Ipsos poll, https://www.reuters.com/article/us-health-coronavirus-usa-poll/most-americans-would-take-coronavirus-vaccine-if-deemed-safe-reuters-ipsos-poll-idUSKBN22I019 (2020).

24. Kartoglu UH, Moore KL, Lloyd JS. Logistical challenges for potential SARS-CoV-2 vaccine and a call to research institutions, developers and manufacturers. *Vaccine* 2020; 38: 5393–5395.

25. COVID-19 vaccine: From the lab to your doorstep. *Deutsche Welle*, https://www.dw.com/en/coronavirus-covid-19-vaccine-ups-astrazeneca-oxford/a-54691039.

26. Kaiser J. Temperature concerns could slow the rollout of new coronavirus vaccines. *Science News*, https://www.sciencemag.org/news/2020/11/temperature-concerns-could-slow-rollout-new-coronavirus-vaccines. (2020).

27. Gilbert JA. Seasonal and pandemic influenza: Global fatigue versus global preparedness. *The Lancet Respiratory Medicine* 2018; 6: 94–95.