

The Determinants of COVID-19 Vaccine Development Success

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Executive Summary

The enormous costs in lives and economic disruption wrought by the SARS-CoV-2 virus (COVID-19) suggest that there are significant social returns to the development of therapeutics that effectively prevent or treat infections. Indeed, in the early days of the pandemic much of the public discussion about regaining our health and our wealth was centered on the successful development of a vaccine.

Two years from the first reports of the emergence of a novel infectious disease, multiple vaccines that are safe and effective in preventing COVID-19 infection and reducing deaths from infection are available. As of December 31, 2021 there are 33 emergency authorized or approved vaccines, including four widely distributed in Western countries and numerous others available in other countries. Many other vaccine candidates are still in development worldwide. The current public discourse has now moved on to consider how best to allocate vaccines to all who might benefit from initial and ongoing access to them.

The rapid development of multiple safe and effective COVID-19 vaccines appears to be both testament to the unparalleled current state of scientific expertise and quite curious. Successful vaccine development, like other therapeutics, is known to be costly, risky and uncertain. Moreover, some market failures uniquely plague vaccine development in the midst of an emergent pandemic caused by a heretofore unknown virus.

This report examines the conditions of COVID-19 vaccine success from an economic perspective. I specifically seek answers to two questions: first, what are the drivers of successful COVID-19 vaccine creation and conversely, the drivers of vaccine failure; and, second, how do these drivers matter in the specific experiences of COVID-19 vaccine candidates? To answer these

questions, between May 2021 and December 2021, I conducted an in-depth literature review, interviewed key stakeholders and conducted case studies on specific COVID-19 vaccines. Stakeholders were selected for interview from public documents of COVID-19 vaccine candidate developers, funders, and a mix of multidiscipline scholars in biology, immunology, virology, economics, law, manufacturing and regulatory science. I selected vaccine case study candidates to investigate using public documents drawn from the gray literature and shareholder reports. I took care to choose candidates among those that are currently approved, abandoned or still in development and from a cross section of vaccine platforms and originating countries and geographical regions.

The nine drivers of COVID-19 vaccine success I ultimately identified characterize the current organization, financing and regulation of vaccine development. They include: pre-pandemic investments in open science related tools and collaborations, pre-pandemic knowledge of coronaviruses and technological development of vaccine platforms; regulatory infrastructure; collaboration and harmonization across agencies and countries; the ability to hold intellectual property, license intellectual property across entities and enter into partnership arrangements across universities and private firms; the willingness of funders to underwrite the significant costs and risks entailed in the development of new vaccines across technologies; innovator activities and countries; advanced purchase arrangements to guarantee revenue to innovators for vaccines after development and regulatory approval; and innovators pursuit of manufacturing at scale and “at risk” including through partnerships with external contract manufacturers before and after regulatory approval. Each of these drivers were repeatedly raised as important by the developers and funders of these efforts themselves. Once raised, I endeavored to place these drivers first into the wider context of previous work on the determinants of vaccine success in both non-emergent

and emergent settings and second as a framework for assessing the experiences of specific vaccine candidates. Details of how each of these factors related to specific vaccine candidate development efforts are described in a standalone “Case Study” section of the report. In none of these activities did I endeavor to quantitatively weigh the relative importance of some factors over others in determining success or failure of candidates. Instead, the report, including the case studies, make clear that some drivers are important across efforts, while others are more relevant to selected vaccine candidates.

Generally, I found in the case of COVID-19 that there has been both private sector willingness to rise to the challenge of bringing a new vaccine to market to address an emergent infectious disease threat and a public sector willingness to support pull and push incentives for vaccine success. The response by private sponsors and public institutions to COVID-19 has been unusual in the magnitude of the financing made available, their ‘portfolio’ approach to the support of multiple candidates across disparate platform technologies and previous developer successes and the cooperation between many disparate actors to support all aspects of basic science and applied research, vaccine development, production and manufacturing scale up and scale out to meet the needs of global populations.

Moreover, all of the case study vaccine candidates took advantage of preexisting scientific knowledge of coronaviruses and how to develop vaccines to address them that was already documented and to a large extent available in the public domain. I discovered that intellectual property and in particular the licensing of patents between various corporate, university, nonprofit and other actors within the context of other economic incentives and institutions have played important roles in the successful development and production of currently available COVID-19 vaccines. Specifically, patents granted to governments, university based researchers and private

companies provide much of the knowledge of coronaviruses, the opportunities and challenges inherent in designing vaccines to address these infectious agents and the platform technologies upon which successful COVID-19 vaccines are built. Much of this knowledge predated the COVID-19 pandemic. Patents also have played a role in the development of specific ingredients critical for successful COVID-19 vaccine production. Licensing arrangements between entities holding patents appear to be important drivers of vaccine success, but existing evidence suggests they are highly varied, complex and largely hidden from public scrutiny. Conversely, I have not identified any credible evidence that patents per se have forestalled innovation or COVID-19 vaccine success.

Several institutions appear to have played outsized roles in hastening vaccine candidate successes. I provide details of these institutions in the report. Conceptually, the need for additional opportunities for public sharing of intellectual property associated with vaccine development and production, facilitated by third parties, became more apparent as the scale of the global crises and the tendency for the pursuit of national interests over global interests emerged. Notably, various governments and multi-stakeholder institutions provided additional push and pull incentives, including the underwriting of clinical trials, advanced purchasing commitments, the de-risking of manufacturing activities and indemnifying vaccine sponsors and producers. Additional efforts to address the COVID pandemic built upon the existing edifice of formal contracts and well established scientific, regulatory, financing and governance institutions appears critical to success by providing assurances and building trust among highly diverse entities in a complex and rapidly evolving ecosystem.

Among the vaccine candidates that “failed,” decisions by innovators to abandon development of these candidates appear largely driven by scientific and business rationales. My

review of the extent empirical evidence also suggests there have been some missteps in COVID-19 vaccine development, including but not limited to procurement activities.

The results of this study are relevant to current discussions regarding access to currently available COVID-19 vaccines. They are also of importance for the future development of novel therapeutics to address emergent infectious disease. I identify several important questions for further investigation. First, I discuss the importance of additional transparency among private companies and public sector institutions and multilateral organizations to further characterize drivers of COVID-19 vaccine success. Second, while I do find that the case of COVID-19 pull and push incentives were used in combination and at massive scale, it is possible certain combinations of push and pull activities taken alone or together may be more impactful under specific conditions. Third, vaccine success under current conditions may have uncertain effects on follow on innovation to address emerging variants or new disease targets. Finally, the results of this study suggest there may be a role for forgivable loans, non-dilutive financing and other types of public finance techniques to be further developed and deployed to address emergent endemic and pandemic threats.

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Section 1: Introduction

The novel disease caused by the SARS-CoV-2 virus (COVID-19) is a shock to both our health and our wealth, with more than 5 million dead worldwide as of December 31, 2021^{1,2} and economic disruption that some have estimated as high as more than \$16 trillion.^{3,4} These enormous and unprecedented costs in lives and economic disruption suggest that there are incalculable social returns to the development of therapeutics that effectively prevent or treat COVID-19 infections.

Much of the public discussion about regaining our health and our wealth in the COVID-19 era is centered on the successful development, production and distribution of an effective vaccine to all who might benefit from access. The first part of vaccine success is generally understood to mean the development of a product that is proven safe and efficacious, and consequently given emergency authorization or approval for use in various countries; whereas the second part of success is scaling up vaccine production and scaling out distribution to meet demand for all who may benefit from access. The first part of vaccine success, what I term “development,” is subject to multiple well-described market failures that are largely not unique to a disease with pandemic potential. Specifically, ex ante vaccine development is expensive, risky and highly uncertain. Nevertheless, the degree of difficulty should be understood as being especially great in successfully bringing to market a vaccine for a newly identified infectious disease with pandemic potential. The second part of success, what I term “production” to meet demand for all those who would benefit, is also expensive and technically challenging. Here again, the challenge lies in part because the process of vaccine production is the product itself; this is not unique to infectious diseases with pandemic potential but is unique to vaccines and other therapeutics that are biologically-based, including non-small molecule drugs and

monoclonal antibody-based products. In the midst of this current pandemic, the rewards to successful vaccine development and production are justifiably expected to be great both for innovators and society at large since demand for the product appears assured. However, as we will see *ex ante*—in the early stages of infectious disease identification and characterization—demand for a successful vaccine was less certain and, as a consequence, vaccine development and production could still be underinvested in by private for-profit biopharmaceutical companies.

As of December 31, 2021, there are 33 emergency authorized or approved vaccines, four widely distributed in Western countries and numerous others available in other countries (Table 1). There are also seven vaccines which were developed through the late stages of clinical trials but then discontinued.⁵ While they may be considered ‘failures’ by some, I discovered that some of these products have contributed to currently ongoing efforts to develop vaccines as I will discuss later (Table 1). Although the numbers differ slightly by source, more than 100 vaccine candidates were in development as of September 2021 (Table 2).⁶

This is a remarkable amount of vaccine success in a relatively short period of time and strikingly so, considering past examples. For context, consider, the mumps vaccine was the fastest vaccine developed in the modern era and took four years from isolation of the mumps virus to licensure in 1967.⁷ Moreover, the COVID-19 vaccines already available for use are notably diverse in their platform technologies, including more established traditional vaccine methods such as inactivated viruses and newer methods including viral vector and mRNA methods, which have been rarely or never successfully applied to produce a vaccine to market before COVID-19 (Table 1). Vaccines for COVID-19 which were ultimately abandoned are also diverse in their platform technologies and sponsors, including some private for-profit companies that have had previous success in bringing vaccines to market (Table 1, Table 2). Vaccine

candidates in the pipeline are also diverse in their platform technologies and primary sponsorship, entailing private companies, academics and other multilaterals, as well as numerous government efforts, especially in their country of origin (Table 2).

While availability and production of vaccines has scaled up considerably since the first vaccines became available (Table 3), global equitable access to COVID-19 vaccines and the health and economic assurance of productivity they bring remains foremost in the thoughts among many stakeholders.⁸ Statistics on dose production delivery and capacity (Table 3) and estimated vaccine dose delivery (Table 4) suggests a significant increase in vaccine availability over the past year. Based on these statistics, the World Health Organization (WHO) has suggested that substantial global access to COVID-19 vaccination may be achieved sometime between 2022 and 2024.⁹

The remarkable success of these vaccines and concerns about access to them raises many questions. This report investigates two: first, what are the drivers of successful vaccine creation and the converse the drivers of vaccine failure, and, second, how do these drivers matter in in the specific experiences of successful COVID-19 vaccines? Answers to these questions are relevant to current discussions regarding access to currently available COVID-19 vaccines and also of importance for the future, as the COVID-19 pandemic is a warning of the public health and economic crises awaiting if we do not address the threat of antimicrobial resistance,¹⁰ among other concerns.

Several authors have already discussed likely determinants of COVID-19 vaccine success and specifically the factors that enabled acceleration of development over more expected timelines,¹¹ including previous efforts to address other emerging infectious disease. This speed have been attributed to the sheer magnitude of capital and labor resources devoted to addressing

COVID-19, an intensity of cooperation, encompassing the public and private sectors and occurring both within and across national borders and the use of innovative platform technologies that had already been developed. To be sure, as early as July 2020 more funding had already been poured into COVID-19¹² vaccine development than into the development of any previous vaccine. There is also a long-established economic literature on drivers of therapeutic success. This work largely abstracts from emergent threats to national and international health and wealth including non-pandemic conditions. I draw on these literatures to systematically answer the questions posed in the context of the COVID-19 pandemic.

To conduct this study, I conducted an in-depth review of the peer-reviewed published and gray literature, interviewed stakeholders and key opinion leaders and conducted in-depth case studies of COVID-19 vaccine candidates. I selected case study candidates to profile based on the following criteria: (1) vaccines authorized or approved to date by at least one country's regulator, (2) a group of vaccine candidates that were abandoned in some phase of development or manufacturing by their sponsors to date, and (3) a group of vaccine candidates that are still in development. I took care to choose among candidates based on different vaccine platforms and those originating in various countries and geographical regions. The study began in May 2021, data collection concluded in Fall 2021, and the analyses and report were finalized on December 31, 2021.

The remainder of the report proceeds as follows. Section two provides an overview of the traditional economic view of market failures in therapeutic development and general determinants of vaccine success based on previous literature. Section three provides an overview of how emergent pandemics alter the traditional ways economists may conceptualize vaccine development challenges and incentives aimed to correct these challenges. Section four provides

an overview of COVID-19 vaccine success drivers based on my review of the literature and case studies. I provide more detail regarding drivers of vaccine success that appear to be shared across specific vaccine case studies, which presumably can be generalized to other vaccine candidates still in development. Section five describes the case studies and how they relate to the drivers of vaccine success in detail. Finally, section six summarizes my conclusions, study limitations and discusses important directions for future work.

Section 2: Market failures and vaccine success

This section provides a brief overview of theoretical, conceptual and empirical literature regarding determinants of vaccine success under non-emergent conditions.

Vaccines are unique consumer products and market failures in their success are rife

Vaccines are unique consumer products used to reduce the negative health consequences of infectious disease and viral transmission among individuals. Vaccine success can be conceptualized as a product of a series of steps along a continuum: the application of basic scientific knowledge of the infectious agent to the identification and testing of vaccine candidates, their authorization or approval and their manufacturing, and finally their production to a sufficient scale to meet demand. According to Bown and Bollyky¹³, there are five main steps critical to getting a new vaccine from start to finish, including research and development; clinical trials; production of the drug substance including base ingredients and its formulation into a product; “fill and finish,” or the assembly-line process of putting a vaccine into millions of vials; and then distribution.

Empirical evidence from previous non-COVID-19 projects suggests vaccine development entails a significant amount of costs, risks and uncertainty.¹⁴ It has been estimated that costs associated with vaccine development from discovery to approval fall into a wide range from millions¹⁵ to billions of dollars and take over a decade to complete, with an average chance of failure of 94 per cent.¹⁶ While initial outlays for vaccine research and development may be considered relatively small, the investment needed to conduct large-scale Phase III trials and then build the facilities to manufacture doses at mass scale ranges from \$500 million to \$1.5 billion.¹⁷ Phase III trials of vaccine candidates are the most costly of the clinical trial phases, in part because vaccines are typically intended for use by populations who may be otherwise healthy.

The earliest stages of vaccine development, such as preclinical studies and Phase I clinical trials for establishing safety, are the most risky and prone to failure. However, failures can and do occur in vaccine candidates in later stages of clinical development, including Phase III studies, which establish safety and effectiveness in eligible populations. Many vaccines are also destined for use in children, where the burden of proving that the benefits of vaccination outweigh its harms may be greater than in adult populations. Not all potential harms of vaccines can be detected in the limited context of clinical trials, where the population is selected to conform to narrow specifications that may not match the population that will use the vaccine post-approval. As a result, not only must sponsors of novel vaccines establish safety and efficacy through the completion of clinical trials, they must continue to monitor safety and effectiveness post-approval or post-authorization as a condition of country-specific regulatory approval and liability protections.

The production of vaccines is also expensive and challenging as they are biologics for which the product is the process. There are many opportunities for manufacturing risk for which sponsors must recognize, plan for and mitigate. Vaccine supply entails specialized knowledge, organization and financing to manufacture at scale to meet demand. Many vaccine sponsors will contract with separate companies for the manufacturing of upstream base ingredients, including but not limited to adjuvants—products that “boost” the bodies’ own immune system and support vaccine efficacy—and still other companies downstream for “fill and finish.” Redundancy in the sourcing of base ingredients to adequately meet demand is commonly pursued by vaccine sponsors in Western countries.

Vaccine production by sponsors must meet regulatory requirements to assure purchasers and the public that the product meets or exceeds safety and quality standards for each and every

dose sold before initial authorization and approval is granted by a regulatory body and thereafter vaccine sponsors or their licensees must continue to invest to assure regulators, purchasers and the public that the product is what it purports to contain. Moreover, sponsors of vaccines face country-specific consumer liability requirements for potential clinical harms associated with vaccine use in targeted populations, including product failures in safety, strength or dose, and quality of production.¹⁸

Vaccine sponsors face other nonscientific business determinants of investment in a given product or products to meet demand to address a pathogen, which may ultimately result in a company deciding not to invest or abandoning their existing investments in vaccine development and production. For the majority of potential vaccine sponsors that are part of a for-profit company, any undertaking should expect to realize for the company profit, that is for expected revenue from the sale of the vaccine to meet or exceed the incremental costs of producing the vaccine. Revenue entails the expected price of the vaccine at launch and the expected quantity of sales. Since many purchasers of vaccines are governments, they possess significant purchasing power. Vaccine sponsors may be wary of investment, since governments may insist on substantial price concessions off expected prices. Expected quantities of sales may also be uncertain if the threat subsides or a competitor vaccine launches and becomes preferred over the sponsor's candidate due to safety, efficacy or other characteristics. Moreover, the virus may mutate and the sponsor's vaccine candidate may lose benefit in the face of such changes.

In terms of costs, if the vaccine candidate entails highly specialized production facilities we expect the fixed and variable costs of production to be higher than that of small molecule-based drugs. In addition, the undertaking's profit, costs, risks and uncertainty will be weighed against other opportunities the sponsor could pursue with similar resources. The expenses

associated with investing in a new vaccine candidate can be funded using available resources the company has or can be borrowed from external funders. If the latter financing route is pursued, then outside funds will be borrowed typically from banks and venture capitalists, and those borrowers will expect a rate of return on their capital investments that is equal to the risks and uncertainty of the project and the outside uses of those funds. While more established pharmaceutical companies have access to revenue and capital markets that may be willing to loan them funds to finance vaccine candidate development and manufacturing, early stage biopharmaceutical companies typically face more significant liquidity constraints.

Earlier stage companies also need access to regulatory and manufacturing expertise. Identifying clinical trial endpoints, study inclusion criteria and study design that will be acceptable to meet regulatory requirements for authorization and approval and selecting pathways for market access entails significant expertise that is commonly provided by external parties. In contrast, more established biopharmaceutical companies have the advantage of in-house expertise in how best to overcome development challenges, reduce development risks and uncertainties in establishing product safety and efficacy for regulatory approval, and also enjoy existing resources or relationships with other partners for development activities, production and manufacturing at scale to meet demand. More established companies also face more competing demands on those resources, as the opportunity costs of investing in a vaccine must be weighed against the benefits of investing in potentially more lucrative products where demand is more predictable.¹⁹

Given the expense, risk and uncertainty inherent to vaccine success, vaccine development for known and established pathogens, such as HIV and malaria, is generally understood to be underinvested in by private for-profit biopharmaceutical companies. Moreover, given the costs

and uncertainties delaying investment in vaccine development and production until a product's prospects are more certain can be the most prudent path from the companies' perspective.

For these reasons, before the COVID-19 pandemic there were less than 10 international for-profit biopharmaceutical companies making vaccines for sale in the United States of America and Western Europe, and many stakeholders worried that the existing incentives were too limited to sustain ongoing investment in novel vaccines. In contrast, it is United States and Western European country markets that are the most lucrative for new medicines, driving significant investment. Many established vaccine producers, such as Merck, Pfizer, Sanofi, GSK and Janssen, enjoy significant profit margins on therapeutic products that enjoy patent protection, including in oncology and other therapeutic areas, and can and do channel investments away from vaccines, which tend to be viewed as “low margin” by established companies.

The role of patents in vaccine development

Due to these market failures, intellectual property found largely in the form of patents and less so in trade secrets, are critical determinants of successful biopharmaceutical product development, including vaccines.^{20,21,22,23,24} Patents support innovation by allowing patent holders a limited term right to exclude others.²⁵ This, in turn, allows innovators to charge prices that are above marginal costs of production and, indeed, when vaccines are made by the innovators mentioned above for Western country use, they tend to be higher priced and face limited to no competition, reflecting these protections.

Knowledge required for vaccine development and production made freely available for use

Some types of knowledge for vaccine success may also be freely available for use to all. This knowledge has various names, but here I term this “open science.” There are many tools and techniques to share knowledge freely relevant to vaccine success. Some tools are related to

public institutions and may even be required of scientists wishing to publish their work in peer-reviewed journals such as public registries of gene sequences. Other tools of open science include domestic and international clinical trial registries, preprint services, peer-reviewed publications that are made free for the public to access reporting endpoint validation, preliminary and final trial results among other activities, and publicly searchable patent and clinical trials databases.

Access to tests and assays and base and final product samples for interdependent innovation activities are also tools of open science. Some of these activities might be considered to be particularly important to earlier stages of vaccine identification and validation. Other aspects of open science, including access to testing assays, final product samples and sources of base ingredients may be more important to downstream production activities and manufacturing scale up and scale out.

The “web” of knowledge facilitating vaccine success and licensing

Stakeholders should view vaccines as being the product of a “web” of knowledge; much of the knowledge embodied in a vaccine is held by many actors and some is protected by patents or trade secrets that give the owner exclusive and temporary rights. Of particular relevance to this study is the insight from some recent work suggesting that institutional factors may help facilitate inventions that are complex and embody many different types of knowledge.

One way innovation among patented technology is encouraged in political states that endorse and enforce patents is through the use of licensing between one patent holder and another patent holder. The foundational technology needed to develop a vaccine can be invented in a university lab setting or startup research firm, protected through patents, and subsequently licensed out to a for-profit company, multilateral entity or government for further development

and production. While the entity ultimately receiving the regulatory approval or authorization for vaccine sale may be perceived as the product “inventor” because they transform the foundational technology into the final market product by the public, in practice innovation is multistep, interdependent and multiparty.

When patents are not enough to support vaccine success

The ability to profit off new therapeutics as a monopolist producer for a limited period of time in addition to support from open science may not be enough to induce innovators to invest in the development of new therapeutics to meet demand in non-emergent threats. This may be especially true when the targeted infectious disease are viewed as concentrating among small populations and those with potentially scarce resources to pay for access to a vaccine once brought to market. In the latter circumstances, governments, philanthropists and multilateral organizations have supported various aspects of vaccine candidate identification, testing, manufacturing and distribution to meet demand related to some prioritized threats, such as malaria and HIV.

Pull incentives for vaccine success

Conceptually, patents are a type of “pull” incentive for innovation. There are other types of “pull” incentives that have been used in the context of previous vaccine success.²⁶ For example, states or other purchasers can commit in advance to buy a prespecified quantity of vaccines when they are approved or authorized by regulatory bodies at an agreed to price. The agreed price is typically set to cover at a minimum the product’s development and manufacturing costs. These so-called advanced purchase agreements are the approach taken for childhood vaccines in the United States of America and a number of other countries. When this type of

contract is used for domestic purposes in the United States of America it is sometimes referred to as a “subscription model.”²⁷ An alternative pull approach is an advanced market commitment (AMC), where the price, but not the quantity, of a vaccine to be purchased is agreed to in advance of approval or authorization. Under an AMC, a country or a number of countries and potentially other purchasers commit to a minimum price to be paid per person up to a certain number of individuals immunized. There are a number of advanced market commitments entered into by selected countries and multilateral organizations for therapeutics that prevent or treat infectious disease.²⁸

For both of these alternative pull arrangements, the price of additional purchases can stay the same or change depending on the agreement and prespecified market conditions. These arrangements can and often do set safety and quality standards for a therapeutic to meet. For example, the operative regulatory body approval or authorization for the country or population intended to be served by the product is typically part of this agreement. If no suitable product meeting these prespecified standards were to be developed, no payments are made. However, if a company was successful in making the product but the immediate need for the product subsides, the agreements can still provide some payment to sponsors for their efforts to be rewarded in part. Under both arrangements, subsequent improvements in the product or additional products to aid the effectiveness of the first can also be rewarded by splitting the commitment or adding additional payments.

Pull incentives resolve some of the commitment problems vaccine sponsors perceive in vaccine development. They can also smooth out liquidity constraints for vaccine sponsors and may be particularly helpful for emerging start-up companies in raising other forms of capital to support their development and production efforts.

Push incentives for vaccine success

Push incentives include the government underwriting of research, including but not limited to government-funded research into the biological mechanism of infection and disease, and the support of the establishment of safety of novel product development. Other types of push incentives less commonly used include a government or a non-government multilateral organization underwriting clinical trials to establish vaccine safety and efficacy and the underwriting of manufacturing facilities and base material production to help ramp up and out vaccine production. While much of the former clinical trials related work is typically conducted by universities or multilateral organizations, much of the latter manufacturing related work is commonly conducted by biopharmaceutical companies and other industry vendors.

Section 3: How emergent infectious disease with epidemic or pandemic potential create unique challenges and opportunities for vaccine success

This section provides an overview of how emergent epidemics and pandemics alters the traditional ways economists conceptualize vaccine development challenges and incentives aimed to correct these challenges.

The scientific challenges inherent to bringing a successful vaccine to market is expected to be greater for a new disease, such as COVID-19, in which knowledge of the disease is rapidly evolving at the same time as the virus itself. Emerging pathogens have a way of focusing interest in novel vaccine development by the public, purchasers and governments; vaccine sponsors will be naturally attracted to try to meet such interests and support disease prevention and treatment efforts. Yet, emerging pathogens also present challenges to private for-profit biopharmaceutical company investment due to the uncertainty of whether the emerging threat, and, consequently, the utility of a vaccine to prevent its spread or lessen its health impact, will wane. The risks and costs of investment for vaccine sponsors may be even greater in the midst of a pandemic as manufacturing sufficient doses to meet demand entails both scaling-up production and scaling-out distribution when typically supply chains and labor skilled in these and related tasks may be disrupted.

As a consequence, in the midst of an emerging epidemic or pandemic, assurances may need to be made to private vaccine sponsors that they will be compensated for their investments if the threat resolves or their product is no longer needed. These assurances are usually given by a government, a coalition of governments or multilateral organizations, and private philanthropists and are termed “de-risking” investment activities. When private company

investments are “de-risked,” some of the risks and uncertainties discussed above are in effect transferred from the innovating company to the public or other entity or entities.

In the face of addressing emergent infectious disease with epidemic or pandemic potential in the past several decades, push incentives have almost always been erected alongside pull incentives to support vaccine success.²⁹ For example, during the 2009 H1N1 influenza pandemic, the US government utilized both pull and push incentives to support vaccine success; these included the federal government contracting with vaccine manufacturers in advance for quantity to be supplied at an agreed to price as the sole domestic purchaser, the underwriting of much of the cost of development and production through grants and help with regulators for the product to meet approval standards.³⁰ In the past two decades, the use of both pull and push incentives for vaccine and therapeutic development were also employed to address the threat of anthrax, Ebola and Zika by governments and other funders.

Pull and push incentives on their own have benefits and costs and consequently using them together in the face of emergent pathogens may resolve individual challenges while strengthening opportunities for success. Traditional pull mechanisms alone may be insufficient if they only make commitments for successfully developed and delivered products, forcing the innovative company to absorb all the risk. At the same time, some form of a guarantee of demand for a vaccine once developed has been shown to be needed as an additional incentive and to stimulate ongoing research and development efforts by the private sector.

The important role of trusted third-party institutions in supporting vaccines success in the face of emergent threats

The success of vaccine development against other emergent infectious diseases also underscores the importance of preexisting institutions in building knowledge, facilitating sharing

and cooperation and lending the weight of credibility to such activities. Institutions can also mitigate commitment concerns on the part of multiple parties and reduce other risks and uncertainties uniquely associated with bringing vaccines to market. Institutions can support such activities by establishing norms, supporting open communication, shared responsibilities and enforcement activities.

Stakeholders I interviewed for this report and the case studies I detail below highlight three general types of preexisting institutions important to vaccine success in the face of emergent threats. The first include long-standing regulations administered by regulatory agencies that set standards for vaccine approval and ensure that pharmaceutical companies bringing vaccines to market meet minimum standards for vaccine safety and quality. If and when liability concerns arise with the use of a particular vaccine, regulatory institutions also ensure responsibility is apportioned fairly and victims are compensated. These activities are critical in the face of an emergent threat when desperation and political expediency may lend itself to the loosening of approval and manufacturing standards and calls for broad liability exemptions. Regulatory agencies include but are not limited to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). There are also cross-national efforts to standardize regulatory requirements of novel vaccine and other therapeutics development to address emergent pathogens. They include the World Health Organization's (WHO) prequalification program that provides advice to the United Nations Children's Fund (UNICEF) and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchases by such agencies for vaccination programs they administer.

The second type of institutions are state-sponsored government agencies and multilateral organizations that act to support vaccine development and production at risk. Perhaps the most

notable example of this type of institution relevant to vaccine success in the face of emergent disease is found in the United States of America, but other countries have agencies that serve similar functions. In 2010 the US Congress created a specialized subagency of the Department of Health and Human Services (HHS), the US Biological Advanced Research and Development Authority (BARDA), to support the advanced identification and development of medical countermeasures critical to ameliorating perceived public health and defense threats.³¹ BARDA identifies important areas for product development, funds research and development (R&D) efforts by pharmaceutical companies, and may design, fund or provide other technical assistance in clinical research. Since its inception, BARDA has created and maintained vaccine and other therapeutic manufacturing capacity and by directly contracting for manufacturing and therapeutic supply to be available when the need arises. Prespecified commitments to price or to price and quantity for successful vaccines and other therapeutics can be and has been pursued by BARDA. For example, anthrax therapeutics were among the first projects pursued by BARDA, which contributed to the development and supported the path to manufacturing for three products: Anthim (obitoxaximab), Raxibacumab and Immune Globulin (which is also being tested for use in treating COVID-19). BARDA spent approximately \$200 million to ensure GSK's development, production and supply of the antitoxin Raxibacumab for the Strategic National Stockpile. Currently, the European Union does not have an equivalent agency to BARDA, although in the face of the COVID-19 pandemic the founding of such an institution has been proposed by member countries, this will be discussed below.

Similarly, multilateral organizations representing the joint interests of global actors in the face of emergent threats are instrumental in developing and delivering vaccines and other therapeutics. In terms of post-development purchasing and distribution, the paradigmatic

institution is UNICEF, which has led the supply of vaccines to address childhood disease through its partners for more than 20 years.³² UNICEF has also increasingly steered investment by private and public partners into the development of new vaccines and other technologies to support their vaccination programs. In terms of supporting new vaccine development to address emergent pathogen threats, the paradigmatic multilateral institution active in recent years is the Coalition for Epidemic Preparedness Innovation (CEPI).³³ CEPI was founded in 2017 to advance the development of vaccines for a select set of emerging infectious diseases with epidemic or pandemic potential and with global needs and global access front of mind, rather than representing the interests of individual nations or regions. Created as a result of lessons learned during the 2014 Ebola outbreak in West Africa where there was limited therapeutic efforts to scale up or deploy, CEPI was designed similarly to BARDA in that it can swiftly deploy both push and pull mechanisms to support the development of vaccines and therapeutics to address emergent pathogens threats. One of the ways CEPI supports global access is by requiring successful vaccines produced with its support to be accessible first and foremost to low-resource settings. In addition to these activities, CEPI provides significant technical assistance to vaccine sponsors in meeting regulatory requirements by various oversight bodies, including for WHO prequalification.

Section 4: Drivers of COVID-19 vaccine success

In this section, I summarize the findings of my review of the literature, interviews with stakeholders and the completion of case studies to elucidate the drivers of COVID-19 vaccine success. Specifically, I define the drivers and provide additional background regarding the SARS-CoV-2 virus including some details regarding public knowledge of COVID-19 disease and virus characteristics and a description of various institutions that appear critical to supporting knowledge and other necessary ingredients for successful COVID-19 vaccines. Section 5 provides detailed summaries of the vaccine candidate case studies.

A brief note on empirical methodology

I start with a brief note on the empirical methodology I employed to conduct this study. Stakeholders to interview were drawn from experts in vaccine development and key opinion leaders in the funding and distribution of vaccines identified through my literature search, including executives at numerous pharmaceutical companies engaged in COVID-19 vaccine and therapeutic development and officials in each of the institutions detailed above and discussed below. I conducted the interviews via telephone and video conference between May and September 2021. To select case studies, I reviewed the international registry of clinical trials and clinicaltrials.gov to identify COVID-19 vaccine candidates in development since the inception of the epidemic in January 2020. Other data sources that were useful in conducting this review were COVID-19 vaccine trackers, available through various public sources and the peer-review literature, various preprint services and the shareholder reports of the vaccine developers themselves when available. I selected case study candidates to profile based on the following criteria: (1) vaccines authorized or approved to date by at least one country's regulator, (2) a group of vaccine candidates that were abandoned in some phase of development or

manufacturing by their sponsors to date, (3) and a group of vaccine candidates that are still in development. I took care to choose candidates from different vaccine platforms and those originating in various countries. Data collection began in May 2021 and analysis concluded in December 2021. The study design builds on previous efforts seeking to answer related questions using similar methodological approaches.³⁴

Summary of drivers of COVID-19 vaccine success

Table 5 enumerates the drivers of COVID-19 vaccine success. The drivers can be divided into those that are common across vaccine candidates and ones that appear especially germane to some but not all vaccine candidates. I discuss drivers 4 to 6 as a group since they are closely related to each other.

Driver 1: Open science related to national and international research and scientific collaborations

The SARS-CoV-2 genome mapping by scientists appears unprecedented in its speed and international involvement by scientists working all around the world, which appears to have been supported by numerous open science related tools.³⁵ A Chinese scientist working at the Fudan University and the Shanghai Public Health Clinical Center was the first to successfully sequence the virus, now known as SARS-CoV-2, suspected in sickening people in the Chinese city of Wuhan.³⁶ According to public reports, Professor Zhang Yong-Zhen received the sample on January 3, 2020, he and his team in collaboration with a consortium of scientists working in many countries successfully identified and sequenced the virus by January 5, 2020 and uploaded the genomic sequence of SARS-CoV-2, to the US National Center for Biotechnology Information (NCBI) GenBank (a comprehensive genetic sequence database administered by the NIH) on January 5, 2020. Since public

posting of genomic sequences on GenBank can take time to process, Zhang's colleague, Edward C. Holmes, a scientist at the University of Sydney, expedited the public release of the information by posting the genomic sequence of SARS-CoV-2 to the website [Virological.org](https://virological.org) on behalf of the consortium on January 11, 2020.

It is this public posting that forms the basis of all other public and private efforts to characterize the initial virus and emerging variants. Following Zhang's initial genome posting, scientists mapped about 20,000 viral genomes within three months. One study³⁷ found that more than 23,000 articles, including more than 10,000 research papers, on COVID-19 had been published in scientific journals by the end of June 2020 and that more than 31,000 documents related to COVID-19 were catalogued on PubMed Central by mid-July 2020. Technical information sharing also appears to have rapidly expanded in depth and in breadth during the pandemic.³⁸ By early May 2020, four popular preprint servers, medRxiv, arXiv, bioRxiv and ChemRxiv, had already posted nearly 4,000 COVID-19-related studies spanning disciplines from immunology to biophysics. Additionally, among a selection of leading peer-reviewed journals, the average time between submission and publication of COVID-19-related manuscripts has been documented to be half what was standard³⁹ for those journals prior to the pandemic. A quick search of PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/>) on December 31, 2021 by myself with the keywords "COVID-19" returned an incredible 275,714 documents.

These activities, in turn, appear to have been facilitated by additional tools, techniques and resources supported by numerous governments, multilateral organizations and philanthropists and predating COVID-19. For example, the genetic sequence of the virus and subsequent refinements were publicly shared by scientists working all over the

world and facilitated by various platforms that allow for free posting and free access to information posted. This includes platforms maintained by the NCBI, a multidisciplinary research group composed of scientists, employed by government labs, universities and other multilateral organizations and responsible for maintaining a number of publicly available databases employed by scientists and vaccine developers in the specific case of COVID-19. This includes the GenBank genetic sequence database, which contains sequences submitted by individual laboratories and by data exchange with the international nucleotide sequence databases, European Molecular Biology Laboratory (EMBL) and the DNA Database of Japan (DDBJ). NCBI also developed, funds and maintains BLAST, a program for gene sequence similarity instrumental in identifying genes and genetic features relevant to COVID-19.

Other preexisting international resources that appear to be important to COVID-19 vaccines include the website Virological.org and GISAID (<https://www.gisaid.org/>). The former is “a discussion forum for analysis and interpretation of virus molecular evolution and epidemiology” to generate real-time epidemiological information that is interpretable and actionable by public health bodies hosted online by the ARTIC Network and supported by funds from the Wellcome Trust.⁴⁰ The GISAID Initiative promotes the rapid sharing of genetic sequence and related clinical, epidemiological data associated with human viruses, and geographical as well as species-specific data associated with avian and other animal viruses, to help researchers understand how viruses evolve and spread during epidemics and pandemics. The Initiative is a public-private partnership between the Initiative's administrative arm Freunde of GISAID e.V., a registered multilateral association, and governments of the Federal Republic of Germany, the official host of the GISAID platform, Singapore and the United States of America with support from private and corporate philanthropists and received support from the

European Commission between 2014 and 2017. Notably, GISAID was a partner in the PREDEMICS consortium⁴¹ (Preparedness, Prediction and Prevention of Emerging Zoonotic Viruses with Pandemic Potential using Multidisciplinary Approaches) and leader in the development of databases for “zoonotic viruses with epidemic potential in Europe” and facilitated interdisciplinary studies at European universities and national and international health organizations to compile data on patterns of transmission and disease emergence, and immune mechanisms of protection and novel prevention strategies.

Second, the tools and techniques of gene sequencing and mapping all owe their origin to additional scientific tools, techniques, assays and other materials associated with the Human Genome Project and funded by governments, philanthropists and ultimately private companies, including substantial funds from the US Department of Energy, NIH and the Wellcome Trust in the United Kingdom.⁴² GenBank itself was developed at the Los Alamos National Laboratory (LANL) in the United States of America and later transferred to the National Library of Medicine. These tools include DNA clone libraries, a crucial resource in the development of genome sequencing, sequencing protocols, chemical reagents and enzymes all required to conduct this work, and public SNP libraries that can be accessed and searched⁴³ and have been named in various publications related to characterizing COVID-19.^{44,45}

Driver 2: Pre-pandemic knowledge and technology leveraged by innovators

That scientists and various other stakeholders and policymakers knew enough about coronavirus pre-pandemic to characterize the novel virus based on its taxonomic and genomic relationships to other known coronaviruses suggests the existence of other foundational knowledge. The present outbreak of the coronavirus-associated acute respiratory disease was

quickly identified as being caused by a coronavirus,⁴⁶ designated as SARS-CoV-2 and named coronavirus disease 19 (COVID-19) by the World Health Organization (WHO) in January 2020 “due to its taxonomic and genomic relationships with the species severe acute respiratory syndrome-related coronavirus.”⁴⁷

What scientists already knew at the time of the initial reporting of the outbreak was that coronaviruses (CoVs) are a family of enveloped positive-strand RNA viruses infecting vertebrates, named for the crown-like spikes on their surface.⁴⁸ Coronaviruses belong to the family *Coronaviridae* and the order *Nidovirales* and can widely spread in humans, other mammals and birds, and cause respiratory, intestinal, liver and nervous systems diseases, among others.⁴⁹ Human coronaviruses (HCoVs) were first identified in the mid-1960s. Seven common HCoVs are CoV-229E (alpha coronavirus), CoV-NL63 (alpha coronavirus), CoV-OC43 (beta coronavirus), CoV-HKU1 (beta coronavirus), severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and current SARS-CoV-2. CoV-229E and CoV-OC43 have been acknowledged as the cause of the common cold in adults since the mid-1960s. At the time of the initial reporting of the pandemic, scientists and other stakeholders also knew that SARS-coronavirus RNA replication is unique, involving two RNA-dependent RNA polymerases.^{50,51} Much of this foundational knowledge was reported in peer-reviewed publications and listed in Pubmed in the early to mid-2000s.

Most of the non-live or attenuated virus-based COVID-19 vaccines target SARS-CoV-2 proteins. Scientists knew at the time of the initial outbreak that coronavirus’ genomes encode four structural proteins involved in various viral processes common to all coronaviruses. They include spike (S), envelope (E), membrane protein (M) and nucleoprotein (N) structural proteins.⁵² It is the spike protein that allows the virus to enter into human cells, and the virus

that causes COVID-19 appears to have a unique spike protein sequence, the “furin cleavage” site, initially characterized and published in *Antiviral Research* in April 2020⁵³ and then confirmed subsequently.

Innovators, including private companies, leveraged preexisting knowledge related to coronaviruses paired with vaccine platform technologies developed to target other infectious disease including HIV, pandemic flu and other threats to public health to support specific COVID-19 vaccine development in several ways.⁵⁴ For example, Harris has reported that HIV-related vaccine and therapeutic development efforts have had an outsized impact on vaccine development in general in the intervening time periods and specifically led to COVID-19 vaccine success.⁵⁵

In addition, numerous reports suggest it is notable that SARS-CoV-2 is the third novel *Betacoronavirus* in the past 20 years to cause substantial human disease.⁵⁶ Coronaviruses have long been predicted to have a high probability of causing zoonotic disease and pandemics, and, as a consequence, US pandemic preparedness efforts at least since 2000, including medical countermeasure investments, had funded basic scientists at the NIH and NIAID and academic researchers at various universities to study MERS-CoV as a prototype *Betacoronavirus* pathogen to optimize vaccine design, dissect the humoral immune response to vaccination and identify mechanisms and correlates of protection. Moreover, developing antibodies to the prefusion spike protein of coronaviruses had already been considered critical for successful vaccine development pre-COVID pandemic since natural spike proteins in isolation are inherently unstable and do not retain the prefusion shape.⁵⁷ Long before the COVID-19 pandemic, NIH and NIAID scientists working with academic researchers were working on ways to build antibodies to the prefusion spike protein.

Other COVID-19 vaccines are based on pre-pandemic work that had established coronaviruses are RNA-based. The genetic instability of RNA viruses has long been considered a challenge to develop effective vaccines to mitigate the effects of such viruses.⁵⁸ Nevertheless, the NIH in collaboration with extramurally funded university researchers and BARDA⁵⁹ in collaboration with private companies had for decades invested in the spike protein technology and the messenger RNA (or mRNA) platform for vaccine development to address emerging infectious disease as well as other diseases of interest including some forms of cancer. It is this technology that is used in the Pfizer/BioNtech, Moderna COVID-19 vaccines and other mRNA vaccines.⁶⁰ Some of this activity is also related to investments for combating pandemic flu and supported in part by governments including the United Kingdom and Germany, and some multilateral institutions and philanthropic organizations mentioned in the preceding section.

Driver 3: Regulatory infrastructure and related activities

As mentioned above, many individual countries have robust regulatory authorities evaluating the safety and efficacy of new vaccines and other therapeutics pre-pandemic. When the pandemic was first reported there was an increased amount of public-private collaboration to support vaccine development in meeting regulatory standards across national borders. The prominent collaboration supporting such activities is the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership.⁶¹ ACTIV is led by the NIH and involves several US governmental agencies, including BARDA, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Department of Defense and the Department of Veterans Affairs. It also involves the EMA and representatives from academia, philanthropic organizations and pharmaceutical companies.

The main goal of ACTIV is to develop a collaborative framework for prioritizing vaccine and drug candidates, streamlining clinical trials and coordinating regulatory processes. In particular, through ACTIV, the NIH has centrally determined the allocation of limited national biomedical resources⁶² such as nonhuman primates and Animal Biosafety Level 3 labs across the prioritized studies. Additionally, ACTIV's partners agreed to contribute their respective clinical trial capacities (for example, access to clinical trial sites and volunteer networks), irrespective of the vaccine or drug candidate to be studied, to increase efficiency, prevent the wasteful duplication of trials and ensure patients' participation in prioritized clinical trials.

ACTIV has been accompanied by intensified coordination among international regulatory authorities, in particular, the FDA, the EMA and other members of the International Coalition of Medicines Regulatory Agencies. Increased coordination in this domain facilitates the rapid sharing of information⁶³ on the landscape of medical products for COVID-19 and associated clinical trials. It also helped better align regulatory approaches to COVID-19 vaccines and specifically decide and communicate thresholds for vaccine approval and pre-authorization in advance of regulatory review. These resources were cited repeatedly by innovators as a critical step in vaccine success, since with these standards communicated in advance and in a coordinated fashion, the individual innovators could marshal resources to help meet these standards and also make decisions about whether to continue to invest in candidates given these standards.

Liability for potential harm related to the use of vaccines post-approval and distribution is also an important regulatory effort. In the United States of America, the enactment of the PREP Act allowed the Secretary of the US Department of Health and Human Services (HHS) to issue a declaration that extends liability protections to entities and individuals who manufacture,

distribute or administer covered medical countermeasures, including vaccines, against a public health threat or emergency. At the time of writing, neither the European Commission nor the World Trade Organization has similar authority to extend indemnity to vaccine manufacturers in the face of a public health threat or national emergency. As a result, vaccine sponsors must enter into individual liability agreements with non-US governments and multilateral organizations. Several people I spoke to in conducting this study suggested this inactivity is viewed as an impediment to the successful distribution of vaccines to all in need.

Drivers 4–6: Willingness of private companies and investors to pursue vaccine development based on preexisting intellectual property and institutions facilitating cooperation

Once the SARS-CoV-2 virus was identified scientists, private corporations, governments and other institutions raced to support vaccine development efforts, which took on even more urgency as the pandemic was declared.⁶⁴ Here I describe some features of these responses that appear to be shared across candidates.

The first feature is cooperation. Much early COVID-19 vaccine development activity appears to have been facilitated by cooperation among and across institutions with preexisting knowledge of vaccine technologies, clinical development activities and capacity, vaccine production techniques and facilities. Notably, the NIH, the Jenner Institute,⁶⁵ the Salk Institute,⁶⁶ many university-based researchers and CEPI, among others, collaborated with private vaccine developers on early vaccine research and development activities. Some of these institutions, notably CEPI, play a more formal role in facilitating cooperation in later stages of the pandemic and vaccine production and distribution.

The second feature is patents among other forms of intellectual property. Numerous stakeholders suggested that it is notable that preexisting arrangements with the US Patent and

Trademark Office enabled the incorporation of patented sequence data into GenBank, which facilitated the pursuit of intellectual property discussions among innovators and investors. Much evidence of the role of intellectual property in successful vaccine development comes from investigative reporting into selected vaccine candidates I describe in the case studies below. More information is currently shielded from public view. For example, the existence and precise content of patents is limited by the timing of patent filing, registration and approval by patent authorities in various countries. Some of this ambiguity may resolve itself in time, as one of the important features of patents are requirements for disclosure and there is a lag between patent filing, granting and public disclosure that is slowly coming into view.

With respect to COVID-19 vaccines, perhaps the most publicly discussed public patents are related to the spike protein technology critical for mRNA vaccine development.⁶⁷ According to a recent report by KEI, the spike protein technology critical for mRNA vaccine development was conceived in 2016 by scientists with the NIH's National Institute of Allergy and Infectious Diseases (NIAID) and the University of Texas.⁶⁸ Specifically, NIH scientists working with academic researchers came up with a particular solution to address the prefusion spike protein antibody development.⁶⁹ They engineered a new way of "freezing" coronavirus spike proteins in the prefusion shape. The prefusion spike protein for an earlier coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), produced a stronger antibody response at lower doses than the naturally occurring protein in mice. The approach required substituting two amino acids with prolines near the central helix and heptad repeat 1; this is often referred to in the literature as the "the 2P approach." The scientists filed a patent application covering this approach. When SARS-CoV-2 emerged, and its genomic sequence was made public and confirmed, public reports suggest the scientists realized the same approach could work for the

new virus. They then filed another patent application. The KEI report suggests 2P technology has been used by various mRNA vaccine candidates, including but not limited to candidates targeting COVID-19. These include Medigen Vaccine Biologics Corp.; Noachis Terra, Inc.; OncoSec Medical Incorporated; BioNtech AG; N4 Pharm UK Limited; Dynavax Technologies; RNAceuticals, Inc.; Sanofi Pasteur; GlaxoSmithKline Biologicals SA; Adimmune Corporation; Vaxess Technologies; Meso Scale Diagnostics, LLC; The Binding Site Group Ltd.; ReiThera Srl; GeoVax, Inc.; ExcellGene SA; and Thermo Fisher Scientific Inc.

Going beyond the 2P approach, a 2021 report published in *Nature* used patent network analysis techniques to detail the complex web of patents and licensing deals surrounding COVID-19 vaccine development.⁷⁰ The authors identified patents that were relevant to various vaccine technology platforms and used US Securities and Exchange Commission (SEC) filings to identify pertinent licensing deals. The authors identified mRNA-based vaccine candidates for COVID-19 developed by Moderna, Pfizer/BioNtech, CureVac and Arcturus using mRNA technology. All of these technologies involve patents held by various entities including but not limited to the 2P technology discussed above. They include patents related to lipid nanoparticles used to deliver the mRNA to the cells to avoid mRNA degradation. The candidates also cite patents related to delivery system technology required to achieve a desired biological response, some of which appear to have been licensed by Moderna from several other companies.

Among these critical aspects of mRNA vaccine delivery know-how, ownership of the lipid nanoparticle technology appears most important. For the mRNA to be delivered into human cells and give instructions it must be wrapped in microscopic fragments of fat known as lipids.⁷¹ This delivery mechanism was not made by Moderna, Pfizer/BioNtech or other mRNA vaccine candidates but rather originally developed by Canadian scientists for which a complex

web of patents are held by universities and private companies⁷² and in turn licensed out to mRNA vaccine manufacturers.

From this work, we also know that the Moderna vaccine relied on some early work on lipid nanoparticles that was done jointly by the University of British Columbia and Arbutus Biopharmaceuticals in 1998.⁷³ SEC filings show that patents relating to this early technology were solely assigned to the University of British Columbia and then licensed back to Arbutus. Further analysis reveals that in 2012 Arbutus licensed a set of patents relating to the delivery of nucleic acids to Acuitas Therapeutics. In 2016, Acuitas entered into a development and option agreement with CureVac, which included access to patents on lipid nanoparticle technology. Acuitas also granted a sublicense to Moderna; however, in 2016 Arbutus declared that Acuitas's sublicense to Moderna was improper and took to the Canadian legal system for remedy. The litigation in Canada was eventually settled, but in 2018 Moderna began filing challenges to the validity of three of Arbutus's patents, which concluded with the cancellation of claims in two of the three challenges. Moreover, Arbutus also entered into an agreement with Roivant to spin out Genevant, which received a license for the patent portfolio on lipid nanoparticles.

Like Moderna's mRNA vaccine, the Pfizer/BioNtech vaccine requires significant supplies of lipid nanoparticles to encase and deliver the mRNA into the body's cells after inoculation. BioNtech licensed technology from Acuitas but the lipids were then manufactured at scale elsewhere. Genevant also sublicensed some patents to BioNtech, who then entered into an agreement with Pfizer to develop a COVID-19 vaccine.

One interesting example of licensing arrangements facilitating COVID-19 vaccine success relates to Novavax, a company making a vaccine that has only been approved for use in the European Union as of this writing. The Novavax COVID-19 vaccine relies on a specialized

adjuvant excipient from the soap-bark tree of Chile—Matrix-M—which helped stimulate a strong immune responses to the antigen. This adjuvant had pre-pandemic non-COVID-19 purposes, and Novavax originally manufactured it in Sweden. In June 2020, Novavax signed agreements with two other companies to manufacture the adjuvant at the scale needed for its expected vaccine sales. AGC Biologics would produce it at facilities in Denmark and Washington State, as would PolyPeptide Group in California and Sweden. Desert King, another California company, was tasked with acquiring the critical starting material of Matrix-M.

One other interesting example of licensing technology between firms is related to the BioNTech vaccine. Pfizer developed and patented the first stage of the vaccine product, DNA plasmids. Plasmids are then frozen, packed and shipped to other plants where the DNA is turned into the mRNA—the active biopharmaceutical ingredient in the vaccine.

The vaccine case studies also make clear that multiple companies are licensing⁷⁴ their proprietary vaccine adjuvants to other developers. Adjuvants are substances added to a vaccine to improve its immunogenicity, which can reduce the amount of vaccine required per dose, enabling more doses to be manufactured. Adjuvants can also improve vaccine effectiveness in susceptible populations, including older adults. GlaxoSmithKline (GSK), Seqirus and Dynavax have all committed to making adjuvants available for use in novel COVID-19 vaccines developed by other sponsors.

Finally, on the licensing of intellectual property to support COVID-19 vaccine development there are only a handful of systematic sources in the public domain. The majority of these agreements are privately held trade secrets. The Global Healthcare Innovation Alliance Accelerator (GHIAA) is an independent and interdisciplinary think tank that provides research, education, advocacy and support to stakeholders involved with global health agreements and

related policies.⁷⁵ GHIAA has created and curates the MAPGuide, a tool that enables practitioners and policymakers to access and explore analysis of actual and template contractual provisions from global health alliance agreements. The MAPGuide provides links, analysis and commentary on publicly available COVID-19 vaccine agreements. On their website as of December 31, 2021 there are links to two dozen vaccine sponsor contracts with annotations related to specific content.⁷⁶ The vaccines targeted by these contracts are diverse in their platforms and their stage of development. Contracts are also diverse in the involved parties, entailing arrangements between patent holders and between vaccine sponsors, governments and other funders. On their website currently is one contract involving a COVID-19 vaccine (AstraZeneca) and a base ingredient supplier (Fiocruz) entailing technology transfer through a licensing agreement.⁷⁷ However, what is available currently on the website is limited and many, if not most, of the relevant contracts are still not in the public domain.

Driver 7: The willingness of funders to underwrite costs and risks entailed in the development of new vaccines across platforms, companies and countries in advance of approval

Innovators, national governments and multilateral organizations have relied heavily on agreements to fund COVID-19 vaccine development in advance of regulatory approval. Many, but not all funders, have employed a “portfolio” approach to such investments pre-funding vaccine dose delivery across a variety of vaccine platforms and companies. These include the extensive use of advanced purchasing agreements. Here I first highlight several key institutions that entered into advanced purchasing agreements among other funding arrangements common across COVID-19 vaccine case study candidates.

Operation Warp Speed (OWS) and other related government activities supporting vaccine development pre-approval

OWS^{78,79} was launched on May 15, 2020 to accelerate the development, manufacture and distribution of COVID-19 vaccines to serve largely the needs of the US population. OWS is a partnership between the US Departments of Health and Human Services (HHS), including activities stewarded by the subagencies BARDA, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), and the Department of Defense (DOD). Funds supported significant “push” financing to entice major biopharmaceutical companies to prioritize the COVID-19 vaccine market and “pull” incentives through guaranteed purchases for the US population. Specifically, OWS partnered with several private companies to accelerate vaccine development in advance of approval. For example, OWS supported COVID-19 vaccine development by Johnson & Johnson, Oxford/Astra Zeneca, Moderna, Novavax, Merck, Sanofi and GlaxoSmithKline (GSK) across multiple vaccine platforms.⁸⁰

Many details regarding OWS decision-making, investments and spending are not public. Press reporting in Fall 2020⁸¹ indicated that roughly \$2.5 billion had been allocated to general funding to support vaccine development efforts, with the remainder going to advance purchase agreements. It also has been reported⁸² that the total OWS budget in 2020 reached \$18 billion.⁸³ OWS’s spending on these activities appears to sit on top of NIH spending on basic services related to emerging infectious disease including coronaviruses and BARDA spending⁸⁴ on vaccine development and production to treat emerging infectious disease mentioned above. Estimates of direct US government spending on the development, manufacture and advanced procurement of COVID-19 vaccines vary considerably based on data sources included and the timing of data collection, but extant evidence suggests they are unprecedented in their scale and

scope. Recent estimates from the Congressional Research Service, and the Government Accountability Office, provide government spending estimates of between \$18 billion and \$23 billion. Most recently the Congressional Budget Office estimated that the BARDA alone has spent \$19.3 billion on COVID-19 vaccine development to date. To put this spending in perspective, Harris estimates between 2000 and 2019, \$15.3 billion was spent on HIV vaccine research. Eighty percent of this spending was paid for by the US federal government.

As a result of these activities, numerous sources credit the US government's investments in the development of COVID-19 vaccines as accelerating their availability. Other countries pursued similar investment strategies to the United States of America. For example, the German government provided grant support for basic science that turned into a university spin out pre-pandemic, called BioNtech for their own mRNA vaccine platform.⁸⁵ With the advent of the pandemic, the company raised additional financing from the private sector and the German government gave additional support to BioNtech to help with COVID-19 vaccine development. One source reports the German government gave BioNtech \$445 million, enabling the firm to establish proof of principle for their COVID-19 vaccine in sufficient detail to support the partnership with Pfizer. It has also been reported⁸⁶ that the United Kingdom has spent more than \$4 billion, and the European Union has committed even more to support COVID-19 vaccine development. In each of these contexts, funding is divided between financing development and securing vaccine doses using advanced purchasing agreements. Some middle-income countries, such as Brazil and Indonesia, have also made advance purchase arrangements for COVID-19 vaccines.

In contrast, the European Commission⁸⁷ made commitments to COVID-19 vaccines similar to the United States of America in kind and across a variety of vaccine candidates and

platforms but much less in magnitude compared to the commitment of the US government. In June 2020, Brussels launched a €2.7 billion vaccine Emergency Support Instrument (ESI). The ESI provided EU members and Norway the option to purchase an agreed upon amount of vaccines within a given time frame at an agreed price. In return, it supported part of the upfront costs incurred by vaccine suppliers, as a type of ‘down payment’ on vaccines ultimately procured by member states themselves. The size of the ESI will ultimately be surpassed by payments from national governments for the vaccines received. The Commission struck initial vaccine supply deals with several case study vaccine candidates including those pursued by AstraZeneca, Sanofi-GSK, Janssen/J&J, Pfizer/BioNTech, CureVac and Moderna.

CEPI

When COVID-19 emerged, CEPI quickly identified gaps and pursued a portfolio strategy to identify potential therapeutic products to invest in and pivoted to play new and leading roles in the global response. In contrast to the efforts detailed above, CEPI responded to the emergence of the COVID-19 pandemic by targeted vaccine and other therapeutic development that aimed to meet the needs of the low- and middle-income populations and transcend traditional country borders. By the end of January 2020, within three weeks of the publication of the genome sequence for COVID-19, CEPI initiated vaccine development investments with CureVac, Inovio and the University of Queensland, and Moderna, investing \$44 million.

Driver 8: Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch

One main challenge with advanced purchasing agreements is whether and how the vaccine sponsor and funders can provide funding to support manufacturing “at risk” to the vaccine sponsor before the vaccine is approved. That the United States of America and other governments can and did make payments at risk to support unapproved vaccine manufacturing was cited by all stakeholders as a key to COVID-19 vaccine success. As above, the institutions supporting manufacturing efforts at risk tended to provide support across vaccine candidate sponsors and technology platforms employing a portfolio approach. For example, OWS partnered with several private companies to accelerate vaccine manufacturing at scale in advance of approval. OWS supported COVID-19 vaccine manufacturing by Janssen/J&J, Oxford/AstraZeneca, Moderna, Novavax, Merck, Sanofi and GSK across multiple vaccine platforms.⁸⁸ Other countries supported COVID-19 vaccine manufacturing at risk mentioned in the case studies. The European Commission made multiple advance manufacturing deals to help secure COVID-19 vaccine doses for its member nations. In one paradigmatic example, the initial call for producers resulted in a deal with AstraZeneca to provide 400 million doses and a deal with Sanofi-GSK for 300 million doses,⁸⁹ although Sanofi-GSK subsequently halted its vaccine trials. Over 1.2 billion additional doses have been secured by contracts with Janssen/J&J, Pfizer/BioNTech, CureVac and Moderna. While the final financial terms are confidential, the initial funding is believed to represent a significant portion of the European Commission’s €2.7 billion (\$3.2 billion) Emergency Support Instrument, and total spending is likely to be over \$10 billion.

Finally, the rapid development of several mRNA-based vaccines (including those sponsored by Moderna and Pfizer/BioNtech) with a product profile less suited to low-resourced settings, and the ability of the United States of America and other high-income countries to

secure priority rights to post-approval mRNA-based vaccine doses has made clear that there was no single entity charged with global leadership and a mandate to develop and deliver a diversity of innovations needed to support the global response to the pandemic across high-, middle- and low- income settings. To step into this global leadership role, in April 2020, the Access for COVID-19 Tools Accelerator (ACT-A) was launched,⁹⁰ bringing together a coalition of governments, scientists, businesses, civil society, philanthropists and global health organizations (i.e., the Bill & Melinda Gates Foundation, CEPI, Gavi, The Global Fund, Unitaid, Wellcome Trust, WHO, World Bank, UNICEF and PAHO) to expressly support both the manufacture (and equitable distribution discussed further below) of a portfolio of needed pandemic mitigation and therapeutic strategies including vaccines, tests and treatments. ACT-A activities entail threat identification, platform characteristic needs, pull and push incentives for product development, manufacture and distribution, facilitating technology transfer and licensing agreements and support for meeting regulatory standards for vaccine authorization, approval and continuous use. The vaccine portfolio of ACT-A, known as COVAX, was established to accelerate the global supply and equitable access to COVID-19 vaccines for every country in the world. In Fall 2020, COVAX announced their commitment to buying 300 million doses from AstraZeneca and the supply of an additional 200 million doses of the same vaccine from SII paid for by the Bill & Melinda Gates Foundation. In the same announcement, COVAX stated that they intended to distribute vaccines based on member-country population and need, while also maintaining a standing emergency stockpile.⁹¹ One important observation made by several stakeholders is that the key multilateral organizations supporting global access, including COVAX, cannot at the time of writing, support manufacturing efforts by willing companies at risk.

Driver 9: Vaccine sponsor contracts with other manufacturers to scale-up vaccine supply post-approval

One main deficiency of many pre-pandemic advanced purchasing agreements is that they tend to focus heavily on the vaccine sponsor meeting the approval requirements, but less focus on vaccine sponsors or downstream ingredient suppliers meeting quantity commitments in production in specified time periods or by prioritized population. This may be in part because it is hard for to enforce advanced production commitments. COVID-19 has changed this in part because the supply chain for vaccine production is both heavily reliant on multiple parties that themselves face their own constraints related to labor and capital assets in the pandemic and in part because the nationalism exhibited by some countries, including the United States of America, in securing doses in advance of others made more salient countries and funders orientation toward allocation equity. Here I discuss both these issues in more detail, again concentrating on efforts that share commonalities across vaccine candidates including those in the case studies. Also here again, many of the manufacturing support contract and production contracts are not in the public domain at this time and thus a systematic examination of public reports of manufacturing contracts that are in the public domain provides a limited picture. I expect this will resolve over time, as even in the short course of writing this report many more details and systematic collections of information have become available.

Numerous vaccine sponsors have licensed their vaccines to other firms for manufacturing at scale. Perhaps the most noted arrangement is that involving the Serum Institute of India (SII), the world's largest manufacturer of vaccines by volume. Early on in the pandemic, SII made deals with both Oxford/AstraZeneca and Novavax to produce one billion doses of each candidate vaccine by the end of 2021.⁹² At the time of the announcement of this deal, several stakeholders

opined that if this type of collaboration is adopted more broadly, it could have important implications for future vaccine development and global access. The case studies reveal other efforts by various stakeholders to help underwrite manufacturing for COVID-19 vaccine sponsors. ESI also provided significant early down payments on vaccine purchases to further speed development.

I tried to identify a source that systematically details production arrangements for COVID-19 vaccines and located two. Both sources are nonprofit organizations making public the identification, classification and characterization of production contracts licensing arrangements for COVID-19 vaccines currently available or in the pipeline between COVID-19 vaccine innovators and manufacturers. They are the Global Health Centre (GHC) maintained by the Graduate Institute of Geneva and UNICEF (Table 3). Both sources lament the lack of full transparency into these arrangements currently and consequently the contracts they have identified and classified are prone to limitations related to selection bias and potentially non-random missing information. In an early summer 2021 release of their data, both efforts made the distinction between contracts that entail base ingredients, such as “lipids,” adjuvants, excipients and other materials, and ones likely to entail the licensing of intellectual property by one or more entities with others. They suggest that whereas contracts that specify contract manufacturing or so-called “fill and finish” arrangements likely do not entail the licensing of intellectual property from the vaccine sponsor to other manufacturers. However, for our purposes even fill and finish manufacturing arrangements likely entail the transfer of knowledge that could be considered trade secrets by the vaccine sponsor, and consequently marked in agreements as “confidential” or “highly confidential.” In the November 2021 release of the UNICEF data, these distinctions are not provided, but the number of doses contracted for in

agreements between funders and suppliers (Table 4) are provided. The UNICEF effort also reports manufacturing arrangements between vaccine developers and manufacturers. The data reveal the breadth of contracts existing between vaccine sponsors and the very significant amount of vaccine doses secured and delivered or expected to be delivered in the next several quarters.

Section 5: Case studies of COVID-19 vaccine successes and failures

This section provides detailed summaries of the COVID-19 vaccine case studies. Many of the primary documents used in this section are derived from the companies own public statements, including shareholder reports, and various other reports available in the gray and peer-reviewed published literature.

Moderna's Spikevax

Moderna's COVID-19 vaccine is mRNA-based and available in the United States of America, European Union and many other countries under EUA as a two-dose primary series for individuals 18 years of age and older, as a third primary series dose for individuals 18 years of age and older who have been determined to have certain kinds of immunocompromise, and as a single booster dose for individuals 18 years of age and older at least five months after completing a primary series of the vaccine. The vaccine is also authorized for use as a heterologous (or "mix and match") single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID-19 vaccine.

Pre-pandemic knowledge and technology: Moderna is a Cambridge, Massachusetts, US-based biotech start-up. In collaboration with intramural scientists working at the National Institutes of Health (NIH) and other extramural scientists funded by government grants and working at the University of Pennsylvania, among other academic institutions, Moderna invented an mRNA vaccine candidate before the pandemic, but had not successfully brought an mRNA vaccine through to market approval.⁹³ NIH and Moderna entered into an agreement in 2019 to co-develop coronavirus vaccines before the identification and spread of SARS-CoV-2.

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: after the SARS-CoV-2 virus

sequence was made public, the company announced its plans to develop a COVID-19 vaccine in March 2020.⁹⁴

IP, licensing and partnering arrangements: from the onset of their program, Moderna stated COVID-19 vaccine development would be in collaboration with the NIH and various other universities and institutions.⁹⁵ Moderna started building regulatory, clinical trial and manufacturing expertise from scratch and thus relying on collaboration with others after they had developed a proof of concept for their COVID-19 vaccine candidate; they publicly stated this put them at a disadvantage compared to their potential competitors in the COVID-19 vaccine candidate market.⁹⁶ Moderna also had to rely on upstream and downstream licensing arrangements with other companies to obtain key technology for vaccine delivery. Perhaps most notably, the mRNA nature of Moderna's vaccine required the production of large-scale volumes of lipid nanoparticles, for which Moderna collaborated with Corden Biopharmaceutical, a contract manufacturing organization. Moderna had a prior relationship with Corden Biopharmaceutical, producing at Colorado, Switzerland and France sites. Moderna stated publicly that they do not have the in-house capacity to manufacture base ingredients.⁹⁷

Public Citizen identified several patents held by Moderna relating to the appropriate vaccine technologies.⁹⁸ They classified them into several groups based on their description and primary independent claim: patents directed at an mRNA vaccine, patents directed at lipids/NP + mRNA and patents directed explicitly at biopharmaceutical compositions involving lipid NP + mRNA. In their report, they provide a non-exhaustive list of patents related to these categories.⁹⁹ In one recent financial statement, Moderna suggested that it relies to a certain extent on trade secrets, know-how and other technology which are not protected by patents to maintain its competitive position.¹⁰⁰

To date, Moderna's COVID-19 vaccine is the only product that Moderna currently has on the market.¹⁰¹ However, the company has been investigating the expansion of use of this vaccine to other populations and follow-on products, including modifications to their existing vaccine to address emerging variants. In 2021, Moderna announced they had entered into vaccine candidate clinical testing for follow-on COVID-19 vaccines, including those targeted to children and boosters for adults, and for other infectious disease targets.¹⁰² As of the second quarter of 2021, Moderna's COVID-19 vaccine was also undergoing a Phase II/III trial (referred to as TeenCOVE) to determine its effectiveness in children between the ages of 12 to 17. It was determined to be 93 per cent effective in that age group.¹⁰³ Moderna was in the process of enrolling participants for a Phase II/III trial of mRNA-1273 (called KidCOVE) for children between the ages of 6 months to 11 years.¹⁰⁴ At least one of these novel candidate pursuits includes licensing arrangements with other biopharmaceutical companies,¹⁰⁵ including Merck if it meets prespecified criteria.¹⁰⁶

Moderna has also been in the process of developing boosters for SARS-CoV-2 variants.¹⁰⁷ The variant-specific vaccine in development is referred to as mRNA-1273.351. It is designed to fight against the Beta variant (B.1.351). mRNA-1273.351 is undergoing a Phase I clinical trial at the National Institute of Allergy and Infectious Diseases. mRNA-1273.211 is a multivalent booster that is currently in development. It is an amalgamation of both mRNA-1273 and mRNA-1273.351.¹⁰⁸

All three of the vaccines that Moderna developed or is developing (mRNA-1273, mRNA-1273.351 and mRNA-1273.211) were involved in a Phase II study that concluded that a booster dose (half of a normal dose) helped increase the immune response to SARS-CoV-2 and the Gamma, Beta and Delta variants.¹⁰⁹ Moderna also is developing mRNA-1273.617, a booster to

fight against the Delta variant, and proposes mRNA-1273.213, which combines mRNA-1273.617 and another vaccine.¹¹⁰ In Summer 2021, Moderna announced it has established a Research Engine and Early Development Engine to develop boosters and vaccines to fight against any future variants of SARS-CoV-2.¹¹¹

Finally, the company announced preclinical studies to develop 24 additional vaccines, including those targeting Epstein-Barr virus (mRNA-1189), seasonal influenza (mRNA-1010, mRNA-1020 and mRNA-1030), Nipah virus (mRNA-1215) and HIV (mRNA-1644 and mRNA-1574).¹¹²

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: the partnerships Moderna entered into with governments and other stakeholders for COVID-19 are varied and appear at least in part to build on long-standing relationships related to developing vaccine candidates for Zika and HIV with the US government and other international organizations, including the Gates Foundation.¹¹³ Moderna relied on collaborations with the NIH to initiate and conduct clinical trials to meet regulatory standards for market authorization. The company was the first to sign contracts with what later became known as Operation Warp Speed (OWS)¹¹⁴ in February and March 2020, and many but not all of Moderna's contracts precede the founding of OWS.¹¹⁵

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need: Moderna received substantial US government support for vaccine testing and manufacturing.^{116,117} In August 2020, Moderna announced advanced market commitments with staged financing related to meeting prespecified standards in the production and delivery of vaccines for domestic¹¹⁸ and

international use.^{119,120} These agreements include pricing terms post-market launch.¹²¹ The European Commission¹²² also made advanced purchasing commitments to COVID-19 vaccines, including the €2.7 billion vaccine Emergency Support Instrument (ESI) in which EU member countries and Norway were provided the option to purchase an agreed upon amount of vaccines within a given time frame at an agreed price. In return, it supported part of the upfront costs incurred by vaccine suppliers and operated as a “down payment” on vaccines ultimately procured by member states themselves. The European Commission struck initial vaccine supply deals with Moderna.

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: much of this effort was supported by the US government, including contracts with BARDA and OWS and international organizations, including, most notably, support from CEPI.¹²³

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: Moderna stated publicly that they do not have the in-house capacity to manufacture mRNA vaccines to scale.¹²⁴ The fill and finish for Moderna’s vaccine were initially done by Lonza in the United States of America and by Rovi in Spain. Moderna relied heavily on agreements with other entities to manufacture the vaccine candidate for clinical testing and contract manufacturing organizations to scale up and scale out their production before market authorization and after approval in December 2020. Much of this effort was supported by the US government, including contracts with BARDA and OWS, and international organizations, including most importantly support from CEPI. In August 2020, Moderna announced advanced market commitments with staged financing related to meeting prespecified benchmarks in

production and delivery of vaccines for domestic use and international use. These agreements include pricing terms post-market launch.

In the first quarter of 2021, Moderna supplied 88 million doses to the US government, and another 14 million doses were supplied to other governments.¹²⁵ During the second quarter of 2021, Moderna and its contract manufacturing partners supplied the US government with 126 million doses of the COVID-19 vaccine. Seventy-three million doses were supplied to other governments. In total, \$4.2 billion of sales from the COVID-19 vaccine were made in the second quarter of 2021.¹²⁶

In the second quarter of 2021, Moderna announced that Lonza's manufacturing of their mRNA vaccine would double. Additionally, Rovi would be increasing their supply to Moderna as well, along with formulation, fill and finish capabilities. Moderna also will be increasing their own facilities manufacturing of drug substances by 50 per cent. Despite the optimistic projections as to the increasing supply for the vaccine, Moderna does note that due to the highly variable demand for COVID-19 vaccines and booster doses, there remains a risk that supply will not be able to keep up with demand. Particularly of issue is the use of manufacturing partners, Lonza and Rovi, as Moderna will depend upon them to expand their capacity and workers.¹²⁷

Moderna has been investing in increasing their manufacturing capabilities, both in their own facilities and in partner facilities, to match demand for the COVID-19 mRNA vaccine during the second quarter of 2021. Most significantly, they announced an expansion of the Moderna Technology Center (MTC) in Norwood, Massachusetts. The expansion doubles the available production space at the MTC. This will enable Moderna to reach a projected distribution of between 800 million and 1 billion doses in 2021, and up to 3 billion booster doses in 2022.¹²⁸

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: Moderna announced that it would not enforce its patent rights against those making vaccines intended to combat the pandemic. This announcement first occurred before market authorization in the United States of America and was subsequently revised post-authorization and market launch.

Regulatory approval/authorization: the company recognized they were facing significant regulatory risks, as the criteria for authorization and approvals were evolving simultaneously as vaccine candidate identification and testing.¹²⁹ The company received market authorization in the United States of America for their COVID-19 vaccine's use in adults in December 2020, Europe, and many other countries and achieved certification by WHO.¹³⁰ The initial authorization by US and EU regulators is based on final trial results suggesting the vaccine is over 90 per cent effective in preventing severe cases and death.¹³¹ Moderna filed a Biologics License Application with the FDA on June 1, 2021 and wrote in SEC filings that it believed it would be fully approved in August 2021.¹³² Yet, as of December 31, 2021, Moderna's COVID-19 vaccine was still operating in the United States of America under the Emergency Use Authorization (EUA) issued by the FDA on December 20, 2020.¹³³ In Spring 2021, Moderna announced they would be seeking full approval for the vaccine in late summer 2021 or early fall 2021, although as of December 31, 2021, no permission has been granted.¹³⁴ Outside of the United States of America, the European Union and Japan have taken the lead in approving the vaccine for children.¹³⁵ As of December 31, 2021, the Moderna COVID-19 vaccine received Conditional Marketing Authorization in the European Union for ages 12 and up, and was approved for age 12 to 17 by the Japanese Ministry of Health, Labor and Welfare.¹³⁶

J&J/Janssen COVID-19 Vaccine

Janssen Biopharmaceuticals is a Belgium-based division of Johnson & Johnson. The J&J/Janssen COVID-19 vaccine is available in the United States of America, European Union and many other countries under EUA as a single primary vaccination dose for individuals 18 years of age and older and as a single booster dose for individuals 18 years of age and older at least two months after completing primary vaccination with the vaccine. The Janssen COVID-19 Vaccine is also authorized for use as a heterologous (or “mix and match”) single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID-19 vaccine. The J&J vaccine is built off a viral vector vaccine platform.¹³⁷

Pre-pandemic knowledge and technology: pre-pandemic Janssen had an existing partnership with the vaccine maker Crucell, a Netherlands-based company. J&J’s partnership with Crucell was initiated in 2011 and their entry into the vaccine manufacturing business at the time was considered “late” compared to other well-diversified international vaccine manufacturers including Merck, GSK, Sanofi and Pfizer.¹³⁸

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: J&J announced their COVID-19 vaccine candidate on March 30, 2020.

IP, licensing and partnering arrangements: the J&J/Janssen COVID-19 vaccine is a product of academic collaboration for identification and early-stage development activities.^{139,140,141} Janssen Biopharmaceuticals developed the vaccine in collaboration with an academic institution in the United States of America, Beth Israel Deaconess Medical Center of

Boston. Preceding and following the authorization, vaccine manufacturing was primarily the domain of external partners, including collaborations with Emergent BioSolutions to manufacture base ingredients and Catalent to fill and finish.

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: J&J was the second COVID-19 vaccine candidate (after Moderna) to receive US government support for vaccine development, including clinical trials and advanced market commitments for supply to the United States of America.¹⁴²

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need: J&J entered various advanced market commitments with governments and other funders before entering the market.¹⁴³ For example, in December 2020, J&J signed an agreement with Gavi to provide 500 million doses through the COVAX program through 2022. The European Commission¹⁴⁴ also made commitments to the J&J COVID-19 vaccine.

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: initial manufacturing of the vaccine for clinical trials took place at a J&J plant in the Netherlands. However, preceding authorization, vaccine manufacturing was primarily the domain of external partners, including collaborations with Emergent BioSolutions to manufacture base ingredients and Catalent to fill and finish.

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: the J&J COVID-19 vaccine is also a product of numerous internal¹⁴⁵

and external contract manufacturing agreements for the later stage production scale up, which appear to have been initiated early in vaccine candidates development.^{146,147} Following authorization, vaccine manufacturing was primarily the domain of external partners, including continuing collaborations with Emergent BioSolutions to manufacture base ingredients and Catalent to fill and finish. Emergent BioSolutions, one of the contract manufacturers making the viral vector base ingredient, was ordered shortly after authorization by US regulators to stop all production due to emergent safety concerns.¹⁴⁸ In March 2021, J&J announced it was taking over the production of the vaccine and working with the FDA to secure authorization for their plant at about the same time. J&J also announced that they had signed an agreement with Merck—first for fill and finish at a plant in Pennsylvania and eventually for the manufacture of the drug substance at a Merck plant in North Carolina.¹⁴⁹ Both arrangements were facilitated by BARDA.¹⁵⁰

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: J&J remains forthcoming in entering into numerous licensing arrangements to supply vaccines, including technology transfer and the sharing of trade secrets and technical assistance for production. In November 2020, South Africa’s Aspen Biopharmaceuticals agreed to provide J&J with fill-and-finish services. The deal has also been criticized because Aspen had agreed to produce vaccines for Europe while at the same time vaccines were urgently needed in Africa.¹⁵¹ Unfortunately, in June 2021, Aspen had to destroy contaminated doses that had inadvertently been shipped from the US-based Emergent plant, waiting until late July to receive the vaccine from the European plant to bottle instead. This slowed vaccination campaigns in South Africa and elsewhere.

In August 2020, J&J announced an agreement with Biological E. that would also allow

the Indian company to mass-produce the vaccine, entailing the entire manufacturing process. That month, Biological E. purchased a manufacturing plant in Paonta Sahib in Himachal Pradesh from Akorn India, indicating plans to expand its vaccine manufacturing capacity significantly. In February 2021, Reuters reported that Biological E.'s managing director, Mahima Datla, indicated plans to manufacture 600 million doses of J&J vaccine in 2021. Shortly after that Datla reported input shortages. By May 2021, the *Times of India* reported delays had forced Biological E. to change its plans once again. In August 2021, Indian regulators authorized the J&J COVID-19 vaccine for emergency use.¹⁵²

Regulatory approval/authorization: vaccine development relied on in-house regulatory and clinical trials expertise taking advantage of their pre-pandemic experience as the sponsor of other vaccines approved for use in the United States of America. The United States gave J&J's vaccine market authorization in February 2021.¹⁵³ However, the J&J vaccine has encountered additional regulatory challenges. J&J had to temporarily pause its clinical trials in October 2020 after one participant fell ill. In April 2021, FDA halted the use of the J&J COVID-19 vaccine after six women who had taken it—out of 6.8 million doses administered—developed a blood-clotting disorder. The United States of America resumed vaccine use on April 23, 2021, with a warning label about the risk of rare blood clots. While it had been put into use, the European Commission ultimately decided against renewing orders for more J&J COVID-19 vaccine doses beyond 2021.

Pfizer/BioNTech's Comirnaty

Pfizer-BioNTech COVID-19 vaccine, Comirnaty, is an mRNA-based vaccine, authorized for emergency use and available under the EUA in the United States of America, European Union member countries and others as a two-dose primary series for individuals 5 years of age and older, as a third primary series dose for individuals 5 years of age and older who have been determined to have certain kinds of immunocompromise, and as a single booster dose for individuals 12 years of age and older at least five months after completing a primary series of the vaccine. The Pfizer-BioNTech COVID-19 vaccine is also authorized for use as a heterologous (or “mix and match”) single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID-19 vaccine.

Pre-pandemic knowledge and technology: much of the originating technology for the Pfizer/BioNtech vaccine was developed by BioNtech, a biotech firm located in Mainz, Germany, in collaboration with German universities pre-pandemic and also previously patented like the Moderna vaccine. BioNtech and Merck had a prior commercial relationship to develop an mRNA-based vaccine; in August 2018, the companies had signed a collaborative agreement to develop mRNA-based vaccines for the prevention of influenza.

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: at the onset of the pandemic in early 2020, BioNTech invented a candidate mRNA COVID-19 vaccine. On March 17, 2020, the company announced a partnership with Pfizer in which the global biopharmaceutical company would assist in clinical development and manufacturing for all markets outside of China.

IP, licensing and partnering arrangements: the BioNTech vaccine is reliant upon Pfizer's

in-house manufacturing expertise. Pfizer developed and patented the first stage of the drug product, DNA plasmids. The plasmids are frozen, packed and shipped to other plants, where the DNA is turned into mRNA—the active biopharmaceutical ingredient of the vaccine. Bags of filtered mRNA are sent to two additional sites for the last formulation stage, fill and finish. Like Moderna’s mRNA vaccine, the BioNTech vaccine requires vast supplies of lipid nanoparticles to encase and deliver the mRNA into the body’s cells after inoculation. BioNTech/Pfizer has entered into a web of licensing arrangements with other manufacturers to secure access to this technology. Most notably, BioNTech licensed technology from Acuitas, a Canadian firm. In addition, Avanti Polar Lipids of Alabama, a subsidiary of the British company Croda, produced Pfizer’s lipids under a five-year contract signed in November 2021. BioNTech subsequently contracted with firms including Evonik and Merck KGaA to manufacture lipids at facilities within the European Union.

Public Citizen identified several patents claimed by BioNTech relating to the pertinent vaccine technologies.¹⁵⁴ They placed them in three groups based on their description and primary independent claim: patents directed at RNA, patents directed at lipids/NP + mRNA and patents directed explicitly at biopharmaceutical compositions involving lipid NP + mRNA. In a recent financial statement, BioNTech suggested that its patents extend to mRNA structure, formulations and manufacture and rely on trade secrets and confidential know-how to protect several aspects of mRNA manufacturing technology.¹⁵⁵

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: the German government provided grant support for basic science that turned into a university spin out pre-pandemic, called BioNtech, for their own mRNA vaccine platform. With the advent of

the pandemic, the company raised additional financing from the private sector and the German government gave additional support to BioNtech to help with COVID-19 vaccine development. One source reports the German government gave BioNtech \$445 million, enabling the firm to establish proof of principle for their COVID-19 vaccine in sufficient detail to support the partnership with Pfizer.

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need: Pfizer/BioNTech entered into advanced purchasing commitments with the US government,¹⁵⁶ the German government¹⁵⁷ and COVAX to deliver vaccines meeting prespecified characteristics and quantities. The European Commission¹⁵⁸ made advanced purchase commitments to the Pfizer/BioNTech COVID-19 vaccine.

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: Pfizer/BioNtech received help from the US government in resolving emergent manufacturing concerns. Specifically, the companies worried about running short of specific inputs for their existing production facilities. Unlike the other vaccine companies the US government contracted in 2020, Pfizer’s first contract in July was not given a “priority rating” under the Defense Production Act (DPA). Without the priority rating, Pfizer could not jump to the head of the line on supply acquisition. Pfizer reportedly struggled and requested US government help “to give the company better access to roughly nine specialized products it needs to make the vaccine” including lipids.

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: BioNtech entered into a partnership with Shanghai Fosun

Biopharmaceutical to produce and distribute its vaccine in China in March 2020, however, it took until May 2021 to finalize the agreement where the vaccine would be produced at a manufacturing facility owned by Fosun in China. In July 2021, Pfizer and BioNTech entered into a deal with the Biovac Institute in South Africa to use its Cape Town facility to fill and finish the vaccine supplied from plants in Europe for distribution across the African Union beginning in 2022.

Regulatory approval/authorization: the Pfizer/BioNTech vaccine was the first to receive authorization for emergency use by the FDA, the MHRA and the EMA. Since December 11, 2020, the Pfizer/BioNTech COVID-19 vaccine has been available under EUA in the United States of America in individuals 16 years of age and older, and the authorization was expanded to include those 12 through 15 years of age on May 10, 2021. Comirnaty was also the first COVID-19 vaccine to receive authorization in the European Union. The EMA extended vaccine approval to younger aged individuals shortly thereafter. On August 23, 2021, the FDA granted full approval to the Pfizer/BioNtech COVID-19 vaccine for the prevention of COVID-19 in individuals 16 years of age and older.

AstraZeneca/Oxford University's Vaxzevria

Vaxzevria is a vaccine for preventing COVID-19 in people aged 18 years and older. Vaxzevria is made up of another virus (of the adenovirus family) that has been modified to contain the gene for making a protein from SARS-CoV-2. The vaccine has an efficacy of approximately 60 per cent in preventing COVID-19. The vaccine is authorized for use in the European Union and other countries. It is not authorized for use in the United States of America.

Pre-pandemic knowledge and technology: Oxford University/Jenner Institute's COVID-19 vaccine efforts are predicated on extensive scientific and vaccine development expertise, including previous experience with MERS.¹⁵⁹

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: the Oxford/AstraZeneca vaccine was the first to be announced in development publicly. The Oxford team claimed they started working the day after Zhang's sequence was publicly released, and "over the weekend, they had a prototype vaccine candidate¹⁶⁰ and began manufacturing their vaccine right away".

Most of the initial vaccine identification and production was conducted by Oxford University in collaboration with scientists at the Jenner Institute. The team reported that they launched preclinical testing in various animal models concurrently to speed up the process, including mice, pigs and ultimately rhesus monkeys, to get a "jump start" on planning Phase I clinical trials in humans. The team also planned clinical trials in humans,¹⁶¹ including deciding not to design trials in the elderly, which ultimately entailed risks and controversies;¹⁶² the lack of data has led to many European countries advising against its use on older people. The company recently announced follow-up studies to develop a new vaccine against COVID-19 variants (AZD2816), including human testing in Phase II/III.¹⁶³

The company has also been pursuing the development of COVID-19 therapeutics, however, the results to date have been disappointing.¹⁶⁴ In June 2021, the *Wall Street Journal* reported that AstraZeneca's coronavirus antibody treatment failed in late-stage clinical trials to achieve its primary goal of preventing symptomatic COVID-19 in people recently exposed to the virus, the latest disappointment in a broader search for reliable post-infection therapies. A single

dose of the AZD7442 long-acting antibody treatment was not statistically more effective than a placebo in preventing symptomatic COVID-19 in the trial of 1,121 people in the United Kingdom and the United States of America. Like the vaccine,¹⁶⁵ AstraZeneca is planning two more trials, PROVENT and TACKLE, to continue testing the therapeutic with recruitment complete and ongoing, respectively.

IP, licensing and partnership arrangements: Oxford announced their partnership with AstraZeneca, a British-Swedish biopharmaceutical company with global operations headquartered in Cambridge, England, to scale up and scale out production, complete clinical trials and meet regulatory requirements for vaccine authorization and approval by regulators in Organisation for Economic Co-operation and Development (OECD) countries in April 2020.¹⁶⁶ While pre-pandemic AstraZeneca had experience in producing small molecule medicines, it did not have preexisting vaccine expertise.¹⁶⁷ After the deal was signed between Oxford University and AstraZeneca, public reports suggest AstraZeneca became active in providing contract manufacturing, regulatory expertise and communications for the co-developed COVID-19 vaccine.¹⁶⁸

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: preparations for commercial-scale production started soon after the Oxford/AstraZeneca partnership was finalized. A UK-centric supply chain was encouraged, partially funded and facilitated by the UK government. In addition, in October 2020, AstraZeneca signed a \$1.6 billion contract with the US government under OWS that supported manufacturing at risk as well as advanced purchasing commitments. However, manufacturing and other problems, including

its conduct of clinical trials, the vaccine's demonstrated efficacy in producing immunity¹⁶⁹ and politics,¹⁷⁰ have plagued the company's efforts to bring a COVID-19 vaccine to market.¹⁷¹

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need/Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: after the deal was signed between Oxford University and AstraZeneca, public reports suggest AstraZeneca became active in entering into advanced market commitments with various governments and other funders. The collaboration received very significant UK government, European Union, European Commission and multiparty support from the Bill & Melinda Gates Foundation and GAVI, among others, for vaccine development, including clinical trials, advanced market commitments for production and global supply.¹⁷² The vaccine, based on a viral vector platform, has been considered an essential option for low- and middle-income countries¹⁷³ with less access to cold storage and other requirements of the mRNA vaccines.¹⁷⁴ For example, the European Commission's initial call for COVID-19 vaccine producers resulted in a deal with AstraZeneca to provide 400 million doses. In fall 2020, COVAX announced their commitment to buying 300 million doses from AstraZeneca and the supply of an additional 200 million doses of the same vaccine from SII paid for by the Bill & Melinda Gates Foundation. COVAX announced that they intended to distribute vaccines based on member-country population and need, while also maintaining a standing emergency stockpile. At the end of June 2021, more than 700 million doses of the vaccine had been released by the company to supply to over 170 countries.¹⁷⁵

AstraZeneca also entered into government-supported contracts to develop COVID-19 therapeutics. Although disappointing to date, AstraZeneca has received support from the US

government, potentially exceeding \$700 million to develop the treatment and, if successful, to supply hundreds of thousands of doses in another advanced market commitment.

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: Cobra Biologics UK agreed to produce the drug product in England. CP Biopharmaceuticals was contracted to do fill and finish in Wales. SII, the world's largest manufacturer of vaccines by volume, made deals with Oxford/AstraZeneca to produce one billion doses of each candidate vaccine by the end of 2021.¹⁷⁶ In addition, AstraZeneca, to meet with global demand, has chosen to collaborate with “more than 20 supply partners in more than 15 countries.”¹⁷⁷ Their partners are local manufacturing companies that help with the drug substance, drug product, and finished packaging stages under the supervision of AstraZeneca.¹⁷⁸

Much of the current controversies over the Oxford/AstraZeneca vaccine¹⁷⁹ are related to later stages of development and manufacturing scale up for market authorization and delivery. Oxford University's agreement with a contract manufacturer in early stages led to dosages concerns much later on.¹⁸⁰ In April 2021, the European Commission announced a legal suit against AstraZeneca for failure to deliver the vaccine in sufficient quantities as previously contracted for.^{181,182}

Regulatory approval/authorization: The United Kingdom authorized the vaccine for emergency use on December 30, 2020. India approved the vaccine for emergency use on January 6, 2021, and the EMA allowed its use across the European Union on January 29, 2021.¹⁸³ AstraZeneca did not release its US Phase III trial results until March 22; when it did, it faced almost immediate rebuke; as of December 31, 2021, the vaccine had still not received emergency use authorization in the United States of America.¹⁸⁴ In the second quarter of 2021, the vaccine received special regulatory approval for emergency use in Japan.

CureVac's CV2CoV

CureVac's COVID-19 vaccine has not been approved for use by US, EU or other country regulators at the time of finalizing this report. The company had submitted most required preclinical data as part of the EMA's rolling review process, intended to speed up approvals in 2021. The company pulled its vaccine candidate from EMA consideration in October 2021 to focus on its next-generation COVID-19 vaccine.

Pre-pandemic knowledge and technology: CureVac is a German biotech firm spun out of university discovery and development activities.¹⁸⁵ Like Moderna, CureVac had no previous experience bringing a successful vaccine to market; both previous mRNA-based vaccine candidates, one targeted at rabies, the other at prostate cancer, had both failed in development but earned them a solid reputation among funders.¹⁸⁶ CEPI had funded the company's previous efforts.¹⁸⁷

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: Curevac's vaccine technology was so promising at the outset of the pandemic that the US government promised the company \$1 billion for exclusive rights to its vaccine in March 2020. By June 2020, regulators in Germany and Belgium authorized CureVac's candidate, CVnCoV, to begin clinical trials.

IP, licensing and partnering arrangements: beginning in November 2020, Curevac announced partnerships with selected biopharmaceutical companies and contract manufacturing organizations to license required lipid technology, conduct clinical trials in humans and build out its manufacturing and distribution supply chain.^{188,189} Like the Moderna and Pfizer/BioNTech candidates, the Curevac vaccine requires access to lipid technology for mRNA delivery into

human cells after inoculation and entered into various licensing deals with other companies. CureVac entered into contracts with Novartis, a Swiss-based multinational biopharmaceutical company, and Bayer to conduct base ingredient manufacturing activities. In February 2021, CureVac and GSK announced a partnership; GSK was to help CureVac manufacture the mRNA vaccine, and the two would work together to develop a vaccine to target many strains of the virus at once, projected to arrive in 2022.¹⁹⁰ In August 2021, the company announced promising results for their “second generation” COVID-19 vaccine designed to address the emergence of viral variants, including Beta, Delta and Lambda variants.¹⁹¹ Another company announcement in winter 2021 suggested CureVac had already started to invest in preclinical studies of this follow-on vaccine’s efficacy against other COVID-19 variants¹⁹² and potentially other non-COVID-19 applications as well.

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries/Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need: OWS supported Curevac vaccine development. CureVac received considerable financial support from Germany to develop its COVID-19 vaccine and from CEPI to support its clinical trials, scale up manufacturing and build its manufacturing facilities.¹⁹³ In August 2020, CureVac announced they were in talks with the European Commission to guarantee supply before market authorization or approval.¹⁹⁴ CureVac ultimately entered into advanced purchasing commitments for its vaccine with the European Commission.

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product

launch: CureVac had no manufacturing or distribution expertise to scale up and scale out production for its COVID-19 vaccine clinical trials and manufacturing after authorization or approval. Funds to support these efforts came first from the German government and CEPI and then from other funders. CureVac also has advanced manufacturing contracts with the United States of America, CEPI and COVAX.

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: CureVac had no manufacturing or distribution expertise to scale up production for clinical trials and manufacturing after authorization or approval. Unlike BioNTech and Oxford efforts that solely partnered directly with big international, well-diversified and experienced biopharmaceutical companies, CureVac constructed a network of expertise in manufacturing activities.^{195,196} CureVac entered contracts with Novartis, a Swiss-based multinational biopharmaceutical company, and Bayer to conduct fill-and-finish manufacturing activities for its COVID-19 vaccine.

Regulatory approval/authorization: CureVac's vaccine candidate is mRNA-based but has yet to be authorized or approved for use by any regulatory agency worldwide.¹⁹⁷

Novavax's Nuvaxovid

Novavax's COVID-19 vaccine, Nuvaxovid, was authorized for use to prevent COVID-19 in individuals over the age of 18 by the EMA in December 2021. The vaccine has yet to be approved by any other regulator for use in preventing COVID-19. The vaccine uses particles studded with viral proteins, mixed with immune-boosting compounds. The vaccine is given as two shots, spaced three weeks apart.

Pre-pandemic knowledge and technology: Novavax is a Maryland-based US company

founded in 1987 to develop experimental vaccines. Novavax had preexisting vaccine expertise in response to viral outbreaks, including other coronaviruses such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS). Preclinical testing of the previously developed MERS-CoV vaccine demonstrated strong immunogenicity and 100 per cent protection.¹⁹⁸ Novavax also developed a vaccine for Ebola, which proved highly effective in primate studies. Nevertheless, Novavax was on the verge of bankruptcy before the COVID-19 pandemic and had sold its only factory in 2019.

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: Novavax announced its COVID-19 vaccine candidate in April 2020.

IP, licensing and partnering arrangements: the Novavax COVID-19 vaccine relies on a specialized adjuvant excipient from the soap-bark tree of Chile—Matrix-M—that helps stimulate a strong immune response to the antigen. That adjuvant had pre-pandemic non-COVID-19 purposes, and Novavax originally manufactured it in Sweden. In June 2020, Novavax signed agreements with two other companies to manufacture the adjuvant at the scale needed for its expected vaccine sales. AGC Biologics would produce it at Denmark- and Washington State-based facilities, as would Polypeptide Group in California and Sweden. Desert King, a California company, was tasked with acquiring the critical starting material of Matrix-M. In May 2020, Novavax announced that it was using funding from CEPI to purchase a plant in the Czech Republic (formerly Praha Vaccines, a subsidiary of the Cyrus Poonawalla Group, the parent company of SII) that would allow it to manufacture an expected one billion doses of the drug substance.¹⁹⁹ In the United States of America, a vaccine for clinical trials was initially produced by Emergent BioSolutions. FUJIFILM Diosynth Biotechnologies (FDB) eventually

agreed to handle commercial-scale manufacturing at Texas and North Carolina sites. Novavax also agreed to allow FDB to produce its vaccine at a UK plant under an agreement with the UK government.²⁰⁰

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: based on its previous track record, the US government, CEPI and other funders felt comfortable providing Novavax considerable financial support to help it develop its COVID-19 vaccine candidate. The Novavax vaccine technology is also relatively easier to transfer than that of the mRNA-based vaccines, making it an attractive candidate for plants in developing countries to license and scale up for global manufacturing and distribution. The Novavax vaccine also benefits from not requiring the same cold-storage challenges that made others challenging to deploy in remote areas and low- and middle-income countries.²⁰¹

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need/Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: Novavax’s COVID-19 vaccine clinical trials and manufacturing efforts have been supported by funding from the US government, among other funders,²⁰² and advance market commitments to deliver vaccines post-market approval worldwide. As early as May 2020,²⁰³ the company and CEPI had announced an agreement to support clinical trials and manufacturing efforts in addition to allowing procurement and allocation of its vaccine through worldwide efforts now under discussion as part of the Access to COVID-19 Tools (ACT) Accelerator. The company reportedly received the most significant funding commitment from OWS in the spring of 2020 to support clinical

trials, manufacturing efforts and procurement.²⁰⁴ SII, the world's largest manufacturer of vaccines by volume, made deals with Novavax to produce one billion doses of each candidate vaccine by the end of 2021.²⁰⁵

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: Novavax, like other non-mRNA COVID-19 vaccines, has been very well engaged in licensing deals, including technology transfer, fill-and-finish manufacturing and full production manufacturing with global governments and other funders. Takeda signed on in August 2020 (finalized in February 2021) for Japanese production, with assistance from the government of Japan, as did SK bioscience in South Korea, with assistance from CEPI. In September 2020, Novavax signed similar agreements with Biofabri in Spain and SII in India. In February 2021, Novavax reached an agreement with the Government of Canada to someday produce the vaccine at the National Research Council's Biologics Manufacturing Centre in Montreal. Novavax also contracted with a few other companies to fill and finish its vaccine. Par Sterile Products (Endo) signed on in September 2020 to use its Michigan plant. Later agreements were made with Jubilant HollisterStier in Washington State, Baxter in Germany, and GSK in England.

Regulatory approval/authorization: in December 2020, the company announced the launch of clinical trials to establish the vaccine's safety and efficacy.²⁰⁶ Yet, as of December 2021, despite some publicly announced promising results from clinical trials in June 2021, the Novavax vaccine remains unapproved by many country regulators. Some of these delays appear related to manufacturing challenges. For example, Novavax has delayed its clinical trials twice due to scale up challenges in the past year and recently said it would not meet its production targets to fulfill advanced market commitments with the US government and other funders until

the fourth quarter of 2021.²⁰⁷ In August 2021, the company claimed that raw material shortages for some manufacturers are exacerbating the problem even as other companies were reporting gathering safety stocks of these materials; they also stated the US government was putting its funding on “pause” as it waits for the company to resolve its manufacturing concerns.²⁰⁸ On December 20, 2021, the EMA recommended granting a conditional marketing authorization for Novavax’s COVID-19 vaccine Nuvaxovid to prevent COVID-19 in people from 18 years of age.

Merck

After initial investments, Merck abandoned its non-mRNA COVID-19 vaccine candidates in 2021 to focus on therapeutics and supporting other vaccine development and production efforts.

Pre-pandemic knowledge and technology: founded over a century ago in 1891, Merck is a Kenilworth, New Jersey, US-based multinational pharmaceutical company. Merck had developed a previously approved Ebola virus vaccine that used recombinant vesicular stomatitis virus technology. Merck’s agreement with the Biomedical Advanced Research and Development Authority (BARDA) supported this venture.²⁰⁹ Merck also has successfully developed and marketed numerous other vaccines, including those targeted to prevent pneumonia. Prepandemic, Merck’s experience in vaccine development, clinical trials and regulatory expertise was widely considered highly developed.

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: despite its reputation as a global vaccine developer, with both experience and the finances to tackle the emerging coronavirus, Merck was notoriously late to the search for a COVID-19 vaccine and ultimately abandoned its

candidates in 2021.²¹⁰ In mid-February 2021, amid the spread of the virus, Merck's executives and scientists were split. Some advocated developing a vaccine, projecting that the outbreak would become a global pandemic. However, reportedly senior executives such as Chief Executive Ken Frazier and R&D chief Roger Perlmutter were hesitant to pursue risky vaccine development. They feared detracting from their core business or flourishing projects such as cancer research.^{211,212} Merck's ultimate pursuit of a COVID-19 vaccine candidate that employed technology that the company was already somewhat experienced with represented a larger aim to avoid the high-risk strategy of rivals, who investigated newer and less-proven technology. When the company's COVID-19 vaccine candidates failed, Merck shifted its focus to the development of COVID-19 treatments.

IP, licensing and partnership arrangements: in March 2020, when the coronavirus was officially declared a pandemic, Merck engaged in the vaccine race deeper and started seeking a partner. The company reached out to the University of Oxford, which had continued utilizing cold chimpanzee vaccine technology, a project that Merck had previously dropped in the 2000s. The university's scientists ultimately turned down the proposal. They refused to hand over their intellectual property rights due to Merck's inability to guarantee an affordable supply for low-income countries, despite Professor Bell viewing their deal as the "best on the table at the time."²¹³ As the University of Oxford then turned to AstraZeneca, Merck acquired further partnerships. In May 2020, Merck acquired Themis Bioscience, a Vienna-based privately held biotech company developing a broad pipeline of vaccine candidates using a measles backbone, for which it held exclusive licensing rights. Additionally, Merck partnered with the International AIDS Vaccine Initiative, Inc. (IAVI), a multilateral scientific research organization, to develop

the V590 vaccine candidate for COVID-19 using Merck’s previously-approved Ebola virus vaccine’s recombinant vesicular stomatitis virus technology.²¹⁴

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: Merck’s partnership with IAVI to develop the V590 vaccine candidate for COVID-19 was supported by grants from the Biomedical Advanced Research and Development Authority (BARDA).²¹⁵ OWS also supported COVID-19 vaccine development by Merck.

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need: N/A.

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: N/A.

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: two months after abandoning its own COVID-19 vaccine candidates, in March 2021, the company announced that it would instead help manufacture J&J COVID vaccine authorized by the FDA just a few days prior, using two facilities: one to make the drug substance and one to provide the final fill-and-finish stage.²¹⁶

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: N/A.

Regulatory approval/authorization: Merck continued to conduct human trials and test out its candidate with Themis. Yet, Phase I trial results in January 2021 indicated that the immune response in participants was not sufficient, despite the lack of significant safety issues.²¹⁷ Merck

ultimately abandoned its COVID-19 vaccine candidates, especially in the face of Pfizer's and Moderna's already more successful mRNA-based COVID-19 vaccines.

Sanofi

Sanofi's COVID-19 vaccine candidate developed in collaboration with GSK was announced in early 2020 and abandoned thereafter. In Spring 2021, Sanofi acquired rights to another COVID-19 vaccine candidate employing mRNA technology and started Phase III clinical trials. In late 2021, Sanofi announced it was abandoning this candidate vaccine despite promising trial results.

Pre-pandemic knowledge and technology: founded in 2004, Sanofi-Aventis is a multinational pharmaceutical corporation headquartered in Paris, France. The company is a leader in vaccine development and manufacturing. Sanofi previously engaged in the development of vaccines for infectious diseases ranging from diphtheria to yellow fever.

Willingness of innovators to take risks, costs and uncertainty entailed in the development of new technology to meet demand for COVID-19 therapeutics: Sanofi was hesitant to devote resources to the development of novel COVID-19 vaccines. The company initially perceived these efforts as potentially detracting from its core business. Despite this, in April 2020 announced plans to co-develop a COVID-19 vaccine in collaboration with GSK, which was later abandoned.

In Spring 2021, Sanofi bought Tidal Therapeutics to get access to their mRNA technology that was used to reprogram live immune cells. On May 27, 2021, a Sanofi COVID-19 vaccine using this acquired technology entered international clinical trials to evaluate the efficacy of their COVID-19 vaccine with partial funding from the US government. Sanofi paid

\$130 million for the intellectual property rights for Tidal Therapeutic's technology with an additional \$310 million available if vaccine production was successful. However, in late 2021, Sanofi announced they had decided not to pursue the development of their COVID-19 mRNA candidate into a Phase III clinical study, despite positive preliminary trial results. The company cited business reasons for this product's abandonment, including that there were already on the market extremely effective vaccines to prevent COVID-19. The company announced that they would increase their support for expanding the distribution of already existing COVID-19 vaccines globally.

In May 2021, Sanofi entered into an agreement with Stanford Medical School to further invest in their own mRNA vaccine technology. Stanford is expected to provide the inputs for autoimmune and inflammatory illnesses testing and vaccine developments. To further increase their investments in mRNA-based vaccines for presumably non-COVID uses, on June 29, 2021, Sanofi announced that it will invest approximately €400 million annually in a first-of-its-kind mRNA vaccines Center of Excellence. The Center will work to accelerate the development and delivery of next-generation vaccines by bringing together approximately 400 dedicated employees and integrating end-to-end mRNA vaccine capabilities with dedicated R&D, digital, and Chemistry, Manufacturing and Controls (CMC) teams across sites at Cambridge, Massachusetts (US) and Marcy l'Etoile, Lyon (France).

IP, licensing and partnering arrangements: in April 2020, Sanofi entered a contract with GSK to co-develop a COVID-19 vaccine, with the former creating the antigen, a coronavirus protein to trigger the immune response, to GSK's adjuvant, a molecule used to boost the vaccine's level of protection.^{218,219} This COVID-19 vaccine candidate was ultimately abandoned

by GSK. Sanofi announced in August 2021 that it was acquiring Translate Bio to develop mRNA-based vaccine candidates^{220,221} for new COVID-19 variants and other diseases.²²²

Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries: after fierce competition with other companies for government support, Sanofi and GSK's vaccine was one of the six chosen for funding by OWS. OWS provided \$2.1 billion in exchange for a promised 100 million doses. Of this \$2.1 billion, around half Sanofi allocated to clinical trials and development, while the remaining half was to help scale manufacturing and deliver the doses.²²³

Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need: Sanofi pledged 300 million doses for the European Union and 200 million for COVAX to deliver COVID-19 vaccines to low- and middle-income countries.²²⁴ The European Commission made advanced purchase commitments to the Sanofi-GSK COVID-19 vaccine, including an initial deal with Sanofi-GSK for 300 million doses, although Sanofi-GSK subsequently halted its vaccine trials.

Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing “at risk” pre-product launch: three days after acquiring Tidal Therapeutics and their mRNA technology, Sanofi announced they were building a massive vaccine center that would be fully operational in five years to primarily serve Asian markets. In addition, Sanofi announced in the second quarter of 2021 that they are building a new manufacturing site in Toronto, Canada, which is projected to be fully operational by 2026 to mass-produce flu vaccines.

Innovator contracts with other manufacturers to scale vaccine supply post-approval/authorization: Sanofi has supported numerous other COVID-19 vaccine candidate development and manufacturing efforts to support global access.²²⁵

Regulatory approval/authorization: besides utilizing traditional manufacturing techniques, which are complex and slow compared to speedier and more flexible mRNA ones, Sanofi and GSK experienced a significant setback in their efforts to develop a COVID-19 vaccine in December 2020.²²⁶ The companies used reagents to measure the potency of the antigen from two different manufacturers, both of which were faulty and led to erroneously lower doses in clinical trials. As a result, the data showed an insufficient, weak immune response in people over 50 years old, and the company needed to reformulate its doses to restart trials six months later. The difficulty may have amplified this delay to find a representative sample of unvaccinated people from diverse geographic locations and other relevant factors at this time.²²⁷ Ultimately, Sanofi and GSK pushed back their goals for regulatory authorization from the first half of 2021 to the fourth quarter, and the 200 million doses for COVAX failed to come through.^{228,229}

Section 6: Discussion, Limitations, Next steps

Vaccine development is expensive, risky and highly uncertain. The degree of difficulty in successfully bringing to market a vaccine for a newly identified infectious disease is great. Vaccine production can also be expensive and technically challenging. Remarkably, there are now 33 safe and efficacious vaccines available to prevent COVID-19 and many more in development. Whereas in late 2020 there was significant doubt in the success of vaccine candidates to protect against SARS-CoV-2 virus transmission and associated morbidity and mortality, the discussion has now shifted to how best to scale up and scale out production and distribution to ensure access to the vaccines among all who may benefit.

This study aimed to systematically assess two related questions: first, what are the drivers of successful vaccine creation and the relationship between these drivers, and, second, how did these drivers combine in the specific scenarios of successful and unsuccessful vaccine candidates to address the COVID-19 pandemic?

I find in the case of COVID-19, just like previous experience with Ebola, anthrax and H1N1, there has been both private sector willingness to rise to the challenge of bringing a new vaccine to market to address an emergent infectious disease threat and a public sector willingness to support vaccine success. The response by private sponsors and public institutions to COVID-19 has been unusual in the rapidity and magnitude of the funding and the cooperation between many disparate actors to support all aspects of basic science, vaccines research, development, production and manufacturing scale up and scale out to meet the needs of the global population.

I find other numerous interesting and apparently unique aspects of COVID-19 vaccine success. The diversity of the vaccine candidates in their underlying technology platform is notable. Also notable is the source of these innovative vaccines from corporate collaborations

with university-based research teams and small emerging biotechnology companies without a significant track record in bringing other vaccines to market successfully. Interestingly, the case studies reveal that several manufacturers with highly developed and successful pre-pandemic vaccine expertise, including Merck, Sanofi and GSK, ultimately abandoned their own COVID-19 vaccine candidates, but have supported the efforts of other sponsors in their regulatory, production and manufacturing efforts. These companies' decisions to abandon their own vaccine candidates appears to be largely driven by a combination of scientific and business rationales (Table 6).

The public record is also clear that all of the case study vaccines took advantage of preexisting scientific knowledge of coronaviruses and how to develop vaccines to address them. This knowledge was largely in the public domain and accessible through numerous tools of open science. When COVID-19 was announced, scientists at universities and research institutions worldwide worked collaboratively to characterize the virus and put this information in the public domain; the public accumulation of knowledge regarding the virus, vaccine research and development efforts is very significant in scale and scope. Public efforts also supported various tools for vaccine development, many of which predated the pandemic.

I find that intellectual property and in particular the licensing of patents between various corporate, university, nonprofit and other actors within the context of other economic incentives and institutions has played an important role in the successful development and production of currently available COVID-19 vaccines. Specifically, patents granted to governments, university-based researchers and private companies provide much of the knowledge of coronaviruses, the opportunities and challenges inherent in designing vaccines to address these agents and the platform technologies upon which successful COVID-19 vaccines are built.

Much of this knowledge, some of which was patent protected while others was in the public domain and freely available for use, predates the pandemic. Patents also have played a role in the development of specific ingredients critical for successful COVID-19 vaccine production. Licensing arrangements between entities holding patents appear to be important drivers of vaccine success, but existing evidence suggests they are highly varied, complex and largely hidden from public scrutiny.

It is important to note given the current policy debates that I have not identified any credible evidence that patents per se have forestalled innovation or COVID-19 vaccine success. On the contrary, various entities appear to have enthusiastically engaged in the development of patented knowledge and the sharing of that knowledge through licensing activities. Moreover, I have found that the development of patented technology coexisted with many open science-based tools and techniques. In fact, it is possible that their coexistence was critical to vaccine success. The extant empirical record is very clear that open science in the form of virus gene mapping and other base elements of vaccine candidate identification emerged coincident with SARS-CoV-2 reports and clearly hastened COVID-19 vaccine candidate development. Opportunities for knowledge sharing was facilitated by preexisting institutions, including but not limited to registries, peer-review publications with free access and supported in various ways. Other coexisting pull and push incentives provided by preexisting private, government and multilateral entities contributed to vaccine development and production success.

The need for additional opportunities for public sharing of intellectual property associated with vaccine development and production, facilitated by third parties, emerged as the scale of the global crisis and the tendency for the pursuit of national interests over global interests more fully emerged. Indeed, the US government's pursuit of supply agreements that

prioritized Americans interests through OWS contracts, appear to have hastened other countries pursuit of their own prioritized supply. Indeed, while there is no BARDA-like agency in the European Union, a proposed agency called HERA would prioritize support for EU-based pharmaceutical companies engaged in pandemic therapeutic development efforts and supply EU member countries with resultant development products for emerging pathogen threats.

In addition, several institutions appear to have played outsized roles in reducing the frictions entailed in vaccine development and production and as a consequence hastened success. Specifically, already available COVID-19 vaccines and numerous others in development or abandoned to date were supported by additional push and pull incentives provided by various governments and multi-stakeholder institutions, including the underwriting of clinical trials, advanced purchasing commitments, the de-risking of manufacturing activities and indemnifying vaccine sponsors and producers. The existence of formal contracts, and well-established scientific, regulatory, financing and governance institutions in providing assurances and building trust among highly diverse entities in this complex and rapidly evolving ecosystem appears critical to success. Of particular note here is the importance of prespecified clinical trial endpoints, well established regulatory agencies with pre-existing expertise in assessing the safety and efficacy of novel vaccines and the existence of liability protections extended to innovators. These institutions and their ability to facilitate trust across diverse parties appear to be a less well appreciated contributor to COVID-19 vaccine success and one that builds on noted past successes in addressing Ebola, anthrax and other infectious disease threats albeit at a much larger scale.

While I do find that the case of COVID-19 pull and push incentives were used in combination and at massive scale, this leaves many unanswered questions. It is possible certain

combinations of push and pull activities taken alone or together may be more impactful under specific conditions. It would be of interest to better understand the relative magnitude of contributions to successful vaccine development and production from specific determinants, although in this specific setting it is likely challenging or near impossible for analysts to isolate independent effects using standard econometric methods. It would also be of interest to better understand best practices in licensing intellectual property, in indemnification of vaccine sponsors and producers, and in advanced market commitments and other financial tools. The precondition to further empirical work on this topic is more transparency into these and other agreements supporting successful COVID-19 vaccine development and production. Public posting and analysis of these contracts, including additional patent network analysis, is ongoing and an important direction for future work.

A recent paper by Frank, Dach and Lurie argues that various institutions essentially removed the bulk of traditional industry risks related to COVID-19 vaccine development: (a) scientific failures, (b) failures to demonstrate safety and efficacy, (c) manufacturing risks; and (d) market risks related to low demand²³⁰. These institutions did so by pursuing several related activities for which the sum is greater than its parts. These include the support of preclinical studies to understand the disease and its effects on human health, to characterize viral replication rates, transmission rates and susceptibilities, and to understand likely safety and efficacy of various approaches to preventing or mitigating transmission. It also includes these institutions absorbing the bulk of human testing costs and risk through a set of contracts that paid for the various phases of vaccine testing. Finally, they note these entities reduced manufacturing risk by underwriting capacity investments in many different ways. The US government, other countries and some multilateral organizations largely eliminated market risks for successful vaccine

candidates by employing advance purchase commitments that prespecified desirable vaccine characteristics, prices and quantities to be purchased from vaccine manufacturers and distributed to meet population-specific unmet need when approved or emergency authorized.

I add to this classification two additional activities played by these institutions, private innovator companies and a broader focus on international efforts to bring successful COVID-19 vaccines to market. Specifically, these entities appeared to pursue a “portfolio” approach to knowledge generation and vaccine candidate platforms and approaches, choosing to invest in both complementary and competing activities that appeared promising, rather than choosing one approach among many possibilities. In addition, many of the government institutions continue to serve as trusted third parties in vetting promising platform technologies, facilitating knowledge transfer including the licensing of patents upstream and downstream and making matches between vaccines and other organizations and willing and trusted manufacturers. These institutions also may help enforce private firm activities including but not limited to licensing arrangements, technology transfer agreements and production contracts for COVID-19 vaccine success and ensure vaccine safety, quality and adequate supply. Finally, while Frank, Dach and Lurie’s classification²³¹ relates activities mitigating these risks to specific US government efforts, it is clear other non-US governments, multilateral organizations and philanthropists have played important roles in COVID-19 vaccine success.

On the issue of global access, one defining feature of development and procurement efforts funded for most COVID-19 vaccine candidates studied was that they were pursued on behalf of specific populations. That is, the United States of America was pursuing the support of COVID-19 vaccines primarily for the benefit of Americans, whereas other countries’ support of vaccine candidate development and production were largely focused on securing the benefits of

vaccine access for their populations. The actions of the United States of America in particular to secure vaccine supply to the exclusion or priority over others through advanced purchase agreements among other activities is readily apparent in the public record and notable in its magnitude and diversity of vaccine sponsor targets. Other high-income countries appear to have followed similar practices to secure priority access for their populations but not on the same scale. Moreover, the rapid development of several mRNA-based vaccines (perhaps most notably that sponsored by Moderna and to a lesser degree that sponsored Pfizer/BioNtech) with a product profile less suited to low-resourced settings made clear that there was no single entity charged with global leadership and mandate to develop and deliver a diversity of innovations needed to support the global response to the pandemic across high-, middle- and low-income settings. My review makes clear in a very short time period, CEPI, COVAX and ACT-A have stepped into this global leadership role to admirable effect. How best to support and sustain these efforts to address the current pandemic and expected future threats is a key task for future study and global engagement.

Nonetheless, my review of the evidence suggests there have been some missteps in COVID-19 vaccine success. Arguably, it may be the Oxford/AstraZeneca vaccine that has done the most to fuel the fraught battle over intellectual property and technology transfer with regard to COVID-19 vaccines in which the world is now embroiled. Manufacturing and other problems, including its conduct of clinical trials, the vaccine's demonstrated efficacy in producing immunity and politics, have plagued the company's efforts to bring a COVID-19 vaccine to market. The company's more recent failures to deliver COVID-19 vaccines to the European Commission as promised in 2021 only added to multiple frustrations.

These observations raise some more fundamental concerns. First, given the magnitude and diversity of global de-risking activities, the persistent lack of access to existing COVID-19 vaccines for all those who want them is deeply unfair and unjust. Clearly, the benefits for innovation under political regimes that recognize and enforce patents or other types of protected knowledge should be weighed against their costs in excluding others from the patented invention. Economists generally understand the tradeoff as patents should be understood as aiming to balance incentives for innovation, so-called dynamic efficiency, with incentives for affordability and access related to many manufacturers making the patented product, so-called static efficiency. It is the tension between static and dynamic efficiency that underlies some discussion of patent waivers found in the current public debate regarding expanding global access to successful COVID-19 vaccines.

Here my review of the extent empirical evidence suggests there may be some good news in the early months of 2022. The production contracts that are publicly accessible, my discussions with key stakeholders as well as the case studies seem to suggest that some vaccine sponsors have been much more proactively engaged in supporting global manufacturing and distribution efforts than others. Among the successful vaccine case studies, the outlier appears to be the NIH/Moderna vaccine with their lack of engagement in facilitating global manufacturing capacity and access efforts. However, this observation is limited by the opacity of the public record and may change over time.

Numerous stakeholders interviewed also raised concerns of a different type of vaccine nationalism taking hold, again, largely driven by US efforts. Specifically that when NIH/Moderna have announced support for additional global supply, it has relied on domestic manufacturing to support such efforts, rather than support the scaling up of vaccine

manufacturing by local producers to meet local needs. This is an important area to monitor, as the US government has endorsed other manufacturing efforts that would re-shore or near shore medicine production among many other products. Second, one wonders whether the institutions supporting the pursuit of advanced purchasing and manufacturing de-risking activities could have been more explicit in their support for global access and production as a precondition of initial and ongoing funding. This is an important area for future work, in part because it is non-trivial to structure such future-looking agreements with adequate and enforceable penalties for failure to deliver on agreed to commitments.

There are several previously released reports that are particularly useful to this current study and important for providing the broader context to my study's results. Most notably, a recently released report by Bown and Bollyky details how complex global supply chains for COVID-19 vaccine production emerged to produce the billions of doses of currently available vaccines²³². They argue the separability of vaccine development into various functions affected how the vaccine manufacturing industry was organized heading into the pandemic and conclude that splitting apart the vaccine manufacturing supply chain ultimately affects how many doses can be produced, where and how quickly. Using a case study approach of six COVID-19 vaccines to illustrate these steps, they identify various challenges that may plague manufacturing efforts associated with them. Notably, ensuring that upstream base ingredient manufacturers and downstream fill-and-finish manufacturers can safely and reliably produce the product every single time to meet regulatory standards entails significant risks and uncertainties, especially in the context of country-specific vaccine liability concerns.

This report echoes some of Bown and Bollyky concerns²³³. For example, one related challenge raised by numerous stakeholders I spoke with was the availability of assays, adjuvants,

other base ingredients and samples of existing already approved or emergency authorized vaccines to facilitate manufacturing scale up and scale out among willing partners. Here again, it was suggested that the willingness of vaccine sponsors and their upstream partners to support such activities is critical, but that willingness to provide this information may vary substantially by sponsor. The opacity of the contracts and whether or not they have been fulfilled makes this analysis subject to many caveats. However, in theory, institutions such as BARDA, other government agencies, CEPI and COVAX may have an important role to play in facilitating such exchanges, including by planning for their eventuality in the contract terms of advanced purchasing and production support agreements. Credible enforcement mechanisms may also need more refinement to support these future efforts. It is encouraging to see announcements of additional local manufacturing capacity becoming available to support vaccine access efforts worldwide. Here, long-term credibility of funding, more advanced planning in the support of licensing activities and indemnification and other commitments to the scaling up of COVID-19 vaccine manufacture and distribution and the maintenance of these activities, assurances and facilities is important to consider and plan for by individual governments, nonprofits and multilateral stakeholders.

It is possible that some of the reluctance to support global access to some mRNA vaccines is related to the fact that these platforms likely have other uses in ameliorating the losses associated with COVID-19, other infectious disease, including influenza and HIV, and other dread diseases, such as cancer. Here, licensing between smaller start-up companies and larger biopharmaceutical companies and more formal merger and acquisition activities may have a role to play in facilitating or impeding follow-on innovation and access. Although much classic work on patents and many lay observers have viewed innovation as a one shot deal—the

de novo product either is developed or is not. However, most scholars and practitioners in this field have recognized that in many contexts innovation is cumulative and interdependent, meaning that many innovations build on multiple past inventions and present-day inventions are inputs into future inventions. Previous empirical work has suggested patents can impede follow-on innovation. Specifically, Williams found that a private firm's (Celera's) ownership of portions of the genome (through a proprietary database, not patents) led to large declines in follow-on research²³⁴.

Mergers can also potential harm follow-on innovation in this market. Stopping product development may be related to scientific challenges or business rationales. Cunningham, Ederer and Ma discovered, using biopharmaceutical industry data, that acquired drug projects are less likely to be developed when they overlap with the acquirer's existing product portfolio, especially when the acquirer's market power is large because of weak competition or distant patent expiration²³⁵. Although the authors do not identify such activity specific to vaccine development, a priori the outsize market, regulatory, manufacturing and liability risks associated with vaccine development and sale, especially for infectious diseases effecting populations facing significant liquidity constraints after product development, make them a potential target of "killer" product development decisions. Companies can also decide to exit from existing products or platforms when demand erodes or the costs of maintaining assets in comparison to other opportunities wane. Here again, government and international institutions such as BARDA, other government agencies, CEPI and COVAX may have an important role to play in facilitating material exchanges to support follow-on innovation both in addressing emerging variants of COVID-19 and other non-COVID applications of the mRNA technology. Government anti-trust and international institutions may also need to consider playing a more

proactive role in supporting a vaccine manufacturing ecosystem that can weather the vicissitudes in funding and consumer demand to best address emerging epidemic and pandemic threats over the next decade and beyond.

Finally, results of this study suggest BARDA, OWS, CEPI and many other government and multilateral funding agencies proactively pursued a portfolio approach to investment across vaccines and therapeutics.²³⁶ The COVID-19 pandemic appears to have broadened potential portfolio investments to include manufacturing commitments and the potential for repurposing products to address emerging threats. The results suggest that there may be a role for the expansion of forgivable loans, non-dilutive financing and other types of public finance techniques to be further developed and deployed to address emergent threats. In part, this would help ensure there are sufficient funds to commit over time and leverage the complementarities of private company investments to advance public sector goals. Moreover, collectivizing funding for new vaccine development over wider populations and using various financing mechanisms to support private sector development efforts can ensure that products with characteristics meeting the needs of specific local populations are supported at a global scale.

This study has some additional limitations. Perhaps most notably, future work should examine more closely the already successfully developed COVID-19 vaccines that emerged from non-Western efforts, including that of China, Russia, India and Cuba and the drivers of their success in development, production and distribution.

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- ⁸⁵ Griffin, R. and D. Armstrong. “Pfizer Vaccine’s Funding Came from Berlin, Not Washington.” *Bloomberg News*. Nov. 9, 2020. Web. Apr. 10, 2022. <<https://www.bloomberg.com/news/articles/2020-11-09/pfizer-vaccine-s-funding-came-from-berlin-not-washington>>.
- ⁸⁶ Gross and Bott, *op. cit.*
- ⁸⁷ Kirkegaard, Jacib Funk. “The European Union’s Troubled COVID-19 Vaccine Rollout.” PIIE. Mar. 15, 2021. Web. Apr. 10, 2022. <<https://www.piie.com/blogs/realtime-economic-issues-watch/european-unions-troubled-COVID-19-vaccine-rollout>>.
- ⁸⁸ See Howard and Wright, *op. cit.*, fig. 1.
- ⁸⁹ Bloom *et al.*, *op. cit.*

⁹⁰ World Health Organization (WHO). “The Access to COVID-19 Tools (ACT) accelerator.” Web. Apr. 10, 2022. <<https://www.who.int/initiatives/act-accelerator>>.

⁹¹ Bloom *et al.*, *op. cit.*

⁹² Callaway, Ewen. “The Unequal Scramble for Coronavirus Vaccines – By the Numbers.” *Nature* 584.7822 (2020): pp. 506–507.

⁹³ The vaccine candidate co-developed by the US National Institutes of Health (NIH) and Moderna, mRNA-1273 SARS-CoV-2, employs the use of lipid nanoparticle (NP) technology to deliver mRNA to cells. Once the lipid nanoparticle is injected into a patient, it travels into the cells and instructs them to produce the SARS-CoV-2 spike protein. The presence of this coronavirus protein is thought to trigger an immune response leading to the production of antibodies. If the patient is infected with coronavirus, the antibodies will identify and bind to the virus, which triggers a series of events resulting in the elimination of the virus.

⁹⁴ Bancel, Stéphane and Lorence Kim. Moderna. Form 10-Q. United States Securities and Exchange Commission. Washington, DC 20549. May 7, 2020. Web. Apr. 10, 2022. <<https://www.sec.gov/Archives/edgar/data/0001682852/000168285220000010/moderna10-q3312020.htm>>. Moderna make this illustrative statement: “In response to the global outbreak of coronavirus, we are pursuing the rapid manufacture of our vaccine candidate, mRNA-1273 for the treatment of SARS-CoV-2, the novel strain of coronavirus that causes coronavirus disease 19, or COVID-19, in collaboration with the Vaccine Research Center and Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases, or NIAID, part of the National Institutes of Health, or the NIH. The Coalition for Epidemic Preparedness Innovations, or CEPI, has funded the Current Good Manufacturing Practices cGMP manufacture of the preliminary clinical batches of the vaccine, and NIAID is conducting a Phase 1 clinical trial in the United States. In addition, we have submitted an Investigational New Drug, or IND, application to the FDA to evaluate mRNA-1273 in Phase 2 and late -stage studies if supported by safety data from the NIH-led Phase 1 study.” “To support the scale-up, we may need to divert significant resources to this program, including in connection with our hiring skilled manufacturing staff to expand manufacturing capacity, engineers to manage process scale-up, and clinical and regulatory staff to support clinical development, which would require diversion of resources from our other programs. To the extent our funding collaborators have discretion over the distribution from time to time of funding commitments, we may not ultimately receive the full amount of committed funds and could be exposed to urgent needs for additional funding to support our manufacturing activities. Our funding collaborators may also impose restrictions on or mandate input as to our conduct of clinical trials, manufacturing activities or distribution activities, which may cause delays in the event of disagreement. In addition, since the path to licensure of any vaccine against COVID-19 is unclear, we may have a widely used vaccine in circulation in the United States or another country prior to our receipt of marketing approval. Unexpected safety issues in these circumstances could lead to significant reputational damage for Moderna and our technology platform going forward and other issues, including delays in our other programs, the need for re-design of our clinical trials and the need for significant additional financial resources.”

⁹⁵ *Ibid.* Moderna make this illustrative statement: “In response to the global outbreak of coronavirus, we are pursuing the rapid manufacture of our vaccine candidate, mRNA-1273 for the treatment of SARS-CoV-2, the novel strain of coronavirus that causes coronavirus disease 19, or COVID-19, in collaboration with the Vaccine Research Center and Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases, or NIAID, part of the National Institutes of Health, or the NIH. The Coalition for Epidemic Preparedness Innovations, or CEPI, has funded the Current Good Manufacturing Practices cGMP manufacture of the preliminary clinical batches of the vaccine, and

NIAID is conducting a Phase 1 clinical trial in the United States. In addition, we have submitted an Investigational New Drug, or IND, application to the FDA to evaluate mRNA-1273 in Phase 2 and late - stage studies if supported by safety data from the NIH-led Phase 1 study.” “To support the scale-up, we may need to divert significant resources to this program, including in connection with our hiring skilled manufacturing staff to expand manufacturing capacity, engineers to manage process scale-up, and clinical and regulatory staff to support clinical development, which would require diversion of resources from our other programs. To the extent our funding collaborators have discretion over the distribution from time to time of funding commitments, we may not ultimately receive the full amount of committed funds and could be exposed to urgent needs for additional funding to support our manufacturing activities. Our funding collaborators may also impose restrictions on or mandate input as to our conduct of clinical trials, manufacturing activities or distribution activities, which may cause delays in the event of disagreement. In addition, since the path to licensure of any vaccine against COVID-19 is unclear, we may have a widely used vaccine in circulation in the United States or another country prior to our receipt of marketing approval. Unexpected safety issues in these circumstances could lead to significant reputational damage for Moderna and our technology platform going forward and other issues, including delays in our other programs, the need for re-design of our clinical trials and the need for significant additional financial resources.”

⁹⁶ In the company’s spring 2020 SEC filings, they make this statement: “In addition, another party may be successful in producing a more efficacious vaccine or other treatment for COVID-19 which may also lead to the diversion of governmental and quasi-governmental funding away from us and toward other companies. In particular, given the widespread media attention on the current COVID-19 pandemic, there are efforts by public and private entities to develop a COVID-19 vaccine as fast as possible, including by Johnson & Johnson, GlaxoSmithKline, AstraZeneca, Sanofi and Pfizer. Those other entities may develop COVID-19 vaccines that are more effective than any we may develop, may develop a COVID-19 vaccine that becomes the standard of care, may develop a COVID-19 vaccine at a lower cost or earlier than we are able to develop any COVID-19 vaccine, or may be more successful at commercializing a COVID-19 vaccine. Many of these other organizations are much larger than we are and have access to larger pools of capital and broader manufacturing infrastructure. The success or failure of other entities, or perceived success or failure, may adversely impact our ability to obtain any future funding for our COVID-19 vaccine development efforts or to ultimately commercialize our vaccine, if approved. In addition, we may not be able to compete effectively if our product candidates do not satisfy government procurement requirements with respect to biodefense products.” Bancel and Kim, *op. cit.*

⁹⁷ In the company’s spring 2021 SEC filings, they make the following statements: “Although we have a dedicated manufacturing facility, we do not have sufficient manufacturing infrastructure to support a global roll-out of mRNA-1273 on our own. For example, we rely on Lonza Ltd. to enable larger scale manufacture of mRNA-1273. As a result, we have formed a strategic collaboration with Lonza Ltd. and will need to form additional collaborations with third parties, including contract manufacturing organizations, government and non-government organizations, and other funding and manufacturing sources to do so. We have formed a collaboration with Catalent, Inc. for large-scale, commercial fill-finish manufacturing of mRNA-1273, and a collaboration with Laboratorios Farmacéuticos Rovi, S.A., or ROVI, for large-scale, commercial fill-finish manufacturing of mRNA-1273 intended in principle to supply markets outside of the U.S. starting in early 2021 at ROVI’s facility in Madrid, Spain. We have not previously ramped our organization for a commercial launch of any product, and doing so in a pandemic environment with an urgent, critical global need creates additional challenges such as distribution channels, intellectual property disputes or challenges, and the need to establish teams of people with the relevant skills worldwide. We may also face challenges with sourcing a sufficient number of raw materials to support the demand for a vaccine. We may be unable to effectively create a supply chain for mRNA-1273 that will adequately support demand.” Bancel, Stéphane and David W. Meline. “Moderna. Form 10-Q.” United States Securities and Exchange Commission. Washington, DC 20549.

2021. Web. Apr. 10, 2022.

<<https://www.sec.gov/Archives/edgar/data/0001682852/000168285221000027/mrna-20210930.htm>>.

⁹⁸ Rizvi, “Leading COVID-19 Vaccine Candidates Depend on NIH Technology.”

⁹⁹ Gaviria, Mario and Burcu Kilic. “mRNA-1273 Vaccine Patent Landscape (for NIH-Moderna Vaccine).” Public Citizen. 2020. Web. Apr. 10, 2022. <<https://www.citizen.org/article/modernas-mrna-1273-vaccine-patent-landscape/>>.

¹⁰⁰ In the company’s 2020 SEC filing, they make the following statement: “If any trade secret, know-how, or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business and financial condition could be materially adversely affected. Failure to obtain and maintain all available regulatory exclusivities and broad patent scope and to maximize patent term restoration or extension on patents covering our products may lead to loss of exclusivity and early biosimilar entry resulting in a loss of market share and/or revenue.” Bancel and Kim, *op. cit.*

¹⁰¹ In the company’s 2021 SEC filing, they make the following statement: “As of June 30, 2021, we had one commercial product authorized for use, our COVID-19 vaccine.” Bancel and Meline, *op. cit.*

¹⁰² In the company’s 2021 SEC filing, they make the following statement: “The Phase 2/3 TeenCOVE study of mRNA-1273 in adolescents ages 12-17 years has completed enrollment in the U.S. An initial analysis of 3,732 participants randomized 2:1 in the TeenCOVE study showed a vaccine efficacy rate of 93% in seronegative participants who received at least one injection (modified intent-to-treat cohort) in a secondary analysis. The median duration for follow-up in this analysis was 53 days following the second dose. mRNA-1273 was generally well tolerated. The majority of adverse events were mild or moderate in severity. No serious safety concerns have been identified to date. The most common solicited local adverse event was injection site pain. The most common solicited systemic adverse events after the second dose of mRNA-1273 were headache, fatigue, myalgia and chills. The Conditional Marketing Authorization (CMA) for our COVID-19 vaccine in the European Union has been expanded to include adolescents 12 years of age and older. In addition, the Japanese Ministry of Health, Labor and Welfare also approved our COVID-19 vaccine for ages 12 to 17. We have filed for an EUA for adolescents with the U.S. FDA as well as with additional regulatory agencies around the world... The Phase 2/3 KidCOVE study of mRNA-1273 in the pediatric population ages 6 months-11 years is currently enrolling. We expect to enroll 12,000 healthy pediatric participants in the U.S. and Canada into this two-part, dose escalation study. In Part 1, each participant ages 2 years to less than 12 years may receive one of two dose levels (50 µg or 100 µg). Also in Part 1, each participant ages six months to less than 2 years may receive one of three dose levels (25 µg, 50 µg and 100 µg). An interim analysis will be conducted to determine which dose will be used in Part 2, the placebo-controlled expansion portion of the study... On February 24, we announced that we had completed manufacturing of clinical trial material for our variant-specific vaccine candidate, mRNA-1273.351, against the SARS-CoV-2 variant known as the Beta variant (or B.1.351, first identified in the Republic of South Africa) and that this vaccine had been shipped to the National Institutes of Health (NIH) for a Phase 1 clinical trial to be led and funded by the NIH’s National Institute of Allergy and Infectious Diseases. We are also developing a multivalent booster candidate, mRNA-1273.211, which combines mRNA-1273 (Moderna’s authorized vaccine against ancestral strains) and the Beta variant in a single vaccine... Data from our Phase 2 study showed that a single 50 µg dose of mRNA-1273, mRNA-1273.351 or mRNA-1273.211 given as a booster to previously vaccinated individuals (n=20 per group) increased neutralizing antibody titer responses against SARS-CoV-2 and important variants of concern, including the Gamma variant (or P.1, first identified in Brazil), the Beta variant, and the Delta variant (B.1.617.2). Neutralizing antibody levels following the boost approached those observed after primary vaccination with two doses of 100 µg of mRNA-1273. These data have been submitted to a peer-reviewed journal for publication. Safety and tolerability profiles following third dose

booster injections of 50 µg of mRNA-1273, mRNA-1273.351 or mRNA-1273.211 were generally comparable to those observed after the second dose of mRNA-1273 in the previously reported Phase 2 and Phase 3 studies. Our Phase 2 study to evaluate three approaches to boosting is ongoing. We are also in the process of developing a booster tailored to the Delta variant (mRNA-1273.617), and anticipate developing a multivalent booster—referred to as mRNA-1273.213—that combines mRNA-1273.617 with another COVID-19 candidate. Our strategy on the dosing for boosters will be informed by ongoing clinical trials that assess mRNA-1273 at the 100 -µg dose against the results seen at the 50 -µg dose, before pursuing an approach with regulatory authorities.” Bancel and Meline, *op. cit.*

¹⁰³ Bancel and Meline, *op. cit.* “The Phase 2/3 TeenCOVE study of mRNA-1273 in adolescents ages 12-17 years has completed enrollment in the U.S. An initial analysis of 3,732 participants randomized 2:1 in the TeenCOVE study showed a vaccine efficacy rate of 93% in seronegative participants who received at least one injection (modified intent-to-treat cohort) in a secondary analysis.”

¹⁰⁴ Bancel and Meline, *op. cit.* “The Phase 2/3 KidCOVE study of mRNA-1273 in the pediatric population ages 6 months-11 years is currently enrolling.”

¹⁰⁵ In the company’s 2021 SEC filing, the company makes the following statement: “We have entered into collaboration agreements with strategic collaborators to accelerate the discovery and advancement of potential mRNA medicines across therapeutic areas. As of June 30, 2021, and December 31, 2020, we had collaboration agreements with AstraZeneca plc (AstraZeneca), Merck & Co., Inc (Merck), Vertex Pharmaceuticals Incorporated and Vertex Pharmaceuticals (Europe) Limited (together, Vertex), and Chiesi Farmaceutici S.P.A. (Chiesi). Please refer to our 2020 Form 10-K under the heading “Third-Party Strategic Alliances” and Note 5 to our consolidated financial statements for further description of each of the collaboration agreements.” Bancel and Meline, *op. cit.*

¹⁰⁶ In the company’s 2021 SEC filing, they make the following statement: “Our prophylactic vaccines modality currently includes ten programs, six of which have entered into clinical trials and demonstrated desired pharmacology, in the form of immunogenicity, in positive Phase 1 clinical trials: H7N9 vaccine (mRNA-1851), RSV vaccine (mRNA-1777), human metapneumovirus (hMPV)/parainfluenza virus type 3 (PIV3) vaccine (mRNA-1653), Zika vaccine (mRNA-1893), CMV vaccine (mRNA-1647) and COVID-19 vaccine (mRNA-1273). We have ongoing Phase 1 trials for the Zika vaccine (mRNA-1893), pediatric RSV vaccine (mRNA-1345), hMPV/PIV3 vaccine (mRNA-1653) and Merck is conducting a Phase 1 trial for an additional RSV vaccine (mRNA-1172), which will be transitioned to Moderna after completion.” Bancel and Meline, *op. cit.*

¹⁰⁷ Juno, Jennifer A. and Adam K. Wheatley. “Boosting Immunity to COVID-19 Vaccines.” *Nature Medicine* 27 (2021): pp. 1874–1875. <<https://www.nature.com/articles/s41591-021-01560-x>>.

¹⁰⁸ Bancel and Meline, *op. cit.* “On February 24, we announced that we had completed manufacturing of clinical trial material for our variant-specific vaccine candidate, mRNA-1273.351, against the SARS-CoV-2 variant known as the Beta variant (or B.1.351, first identified in the Republic of South Africa) and that this vaccine had been shipped to the National Institutes of Health (NIH) for a Phase 1 clinical trial to be led and funded by the NIH’s National Institute of Allergy and Infectious Diseases. We are also developing a multivalent booster candidate, mRNA-1273.211, which combines mRNA-1273 (Moderna’s authorized vaccine against ancestral strains) and the Beta variant in a single vaccine.”

¹⁰⁹ Bancel and Meline, *op. cit.* “Data from our Phase 2 study showed that a single 50 µg dose of mRNA-1273, mRNA-1273.351 or mRNA-1273.211 given as a booster to previously vaccinated individuals (n=20 per group) increased neutralizing antibody titer responses against SARS-CoV-2 and important variants of concern, including the Gamma variant (or P.1, first identified in Brazil), the Beta variant, and the Delta variant (B.1.617.2).”

¹¹⁰ Bancel and Meline, *op. cit.* “We are also in the process of developing a booster tailored to the Delta variant (mRNA-1273.617), and anticipate developing a multivalent booster—referred to as mRNA-1273.213—that combines mRNA-1273.617 with another COVID-19 candidate.”

¹¹¹ Bancel and Meline, *op. cit.* “As of June 30, 2021, we had 24 mRNA development programs in our portfolio with 14 having entered the clinic. We have incurred significant expenses in connection with the discovery, development and commercialization of our products, and we expect to continue to incur significant expenses for the foreseeable future. We anticipate that our expenses will increase significantly in connection with the ongoing development and commercialization of our COVID-19 vaccine and ongoing activities to support our platform research, drug discovery and clinical development, including development of any new generations of boosters and vaccines against variants of SARS-CoV-2, infrastructure and Research Engine and Early Development Engine (which includes our Moderna Technology Center), digital infrastructure, creation of a portfolio of intellectual property, and administrative support.”

¹¹² In the company’s 2021 SEC filing, they make the following statement: “Our four pre-clinical programs within our prophylactic vaccine’s modality is for Epstein-Barr virus (mRNA-1189), seasonal influenza (mRNA-1010, mRNA-1020 and mRNA-1030), Nipah virus (mRNA-1215) and HIV (mRNA-1644 and mRNA-1574).” Bancel and Meline, *op. cit.*

¹¹³ Bancel and Kim, *op. cit.* “In September 2016, we received an award of up to \$126 million from BARDA, to help fund our Zika vaccine program. Three of the four contract options have been exercised. As of March 31, 2021, the remaining available funding net of revenue earned was \$69 million, with an additional \$8 million available if the final contract option is exercised. In January 2016, we entered a global health project framework agreement with the Bill and Melinda Gates Foundation (Gates Foundation) to advance mRNA-based development projects for various infectious diseases, including human immunodeficiency virus (HIV). As of March 31, 2021, the available funding net of revenue earned was \$11 million, with up to an additional \$80 million available if additional follow-on projects are approved.”

¹¹⁴ Bancel and Kim, *op. cit.*

¹¹⁵ *Ibid.*

¹¹⁶ In the company’s spring 2020 SEC filings, they make these statements: “To date, we have financed our operations primarily through the sale of equity securities and revenue from strategic alliances and we cannot be certain that additional funding will be available to us on favorable terms, or at all. Until we can generate sufficient product or royalty revenue to finance our operations, which we may never do, we expect to finance our future cash needs through a combination of public or private equity or debt offerings, structured financings, debt financings, collaborations, strategic alliances, sales of assets, licensing arrangements, and other marketing or distribution arrangements.” “We are working toward the large scale technical development, manufacturing scale-up and larger scale deployment of this potential vaccine through a variety of U.S. government mechanisms such as an Expanded Access Program or an Emergency Use Authorization program. For instance, we received a commitment from the Biomedical Advanced Research and Development Authority, or BARDA, to fund up to \$483 million for our late-stage clinical development programs (assuming the success of the NIAID’s Phase 1 clinical trial of mRNA-1273) and our initiation of a Phase 2 clinical trial of mRNA-1273 under our own IND in the second quarter of 2020, as well as the scale-up of mRNA-1273 manufacture in 2020 to enable potential pandemic response.” Bancel and Kim, *op. cit.*

¹¹⁷ In the company’s fall 2020 SEC filings, they make the following statement: “As part of this effort, we have a commitment from BARDA to fund up to \$954.9 million to enable the initiation of and support the

planning and execution of Phase 2 and Phase 3 clinical trials of mRNA-1273 under our own IND, as well as the scale-up of mRNA-1273 manufacture in 2020 to enable a potential pandemic response.” Bancel and Kim, *op. cit.*

¹¹⁸ In the company’s fall 2020 SEC filings, they make the following statements: “In August 2020, we entered into a supply agreement with the U.S. Government, which we refer to as the U.S. Supply Agreement, for 100 million doses of our vaccine candidate against COVID-19, mRNA-1273, for a total award of up to \$1.525 billion. The total award amount includes approximately \$300.0 million of incentive payments which we will earn if an Emergency Use Authorization or a Biologics License Application, which we refer to as an EUA or a BLA, respectively, is received on or before January 31, 2021. We will receive such incentive payments as product is delivered to and accepted by the U.S. Government. Pursuant to the U.S. Supply Agreement, the U.S. Government made a \$601.4 million upfront payment to us which represents approximately 50% of the fixed price per dose that we are entitled to receive for the committed 100 million doses. We will receive the remaining 50% of the fixed price per dose upon delivery and acceptance of the 100 million doses to the U.S. Government.” Bancel and Kim, *op. cit.*

¹¹⁹ In the company’s fall 2020 SEC filings, they make the following statement: “As of September 30, 2020, we had received cash of \$569.0 million associated with such international supply agreements.” In the company’s spring 2021 SEC filings, the company went on to report: “Subsequent to September 30, 2020, we entered into an additional supply agreement with an international government agency to provide mRNA-1273 supply, our vaccine candidate against COVID-19, up to 50.0 million doses.” Bancel and Kim, *op. cit.*; Bancel and Meline, *op. cit.*

¹²⁰ By spring 2021, these domestic and international commitments to supply vaccines has grown substantially: “We have entered into supply agreements with the U.S. Government, several other governments outside the United States and with UNICEF (on behalf of the COVAX Facility) for the supply of our COVID-19 vaccine. The agreements are generally subject to receipt of authorization or approval for the use and distribution of the vaccine from the relevant regulatory authority in each jurisdiction. Under these agreements, we are entitled to upfront deposits for our COVID-19 vaccine supply, initially recorded as deferred revenue. As of June 30, 2021, we had approximately \$7.2 billion in deferred revenue in connection with the supply agreements with the U.S. Government and other customers, which will be recognized as revenue when revenue recognition criteria have been met.” Bancel and Meline, *op. cit.*

¹²¹ In the spring 2021 Moderna SEC filings, the company makes the following statement: “Pursuant to the U.S. Supply Agreement, the U.S. Government made a \$601.4 million upfront payment to us which represents approximately 50% of the fixed price per dose that we are entitled to receive for the committed 100 million doses. We will receive the remaining 50% of the fixed price per dose upon delivery and acceptance of the 100 million doses to the U.S. Government... The U.S. Government has the option to purchase up to an additional 400 million doses at a fixed price of \$1.65 billion per 100 million doses by specified dates in the agreement.” Bancel and Meline, *op. cit.*

¹²² Kirkegaard, *op. cit.*

¹²³ In Moderna’s spring 2020 SEC filings they make this illustrative statement: “Additionally, our ability to develop an effective vaccine depends on the success of our scaled up manufacturing capability both at our own location and that of our manufacturing partner, which we have not previously tested and which will need to be funded by third parties in order to enable us to have sufficient capacity to respond to a global health challenge. We are also committing financial resources and personnel to the development of mRNA-1273, including to support a scale-up of manufacturing to enable a potential pandemic response, which may cause delays in or otherwise negatively impact our other development programs, despite

uncertainties surrounding the longevity and extent of coronavirus as a global health concern. Our business could be negatively impacted by our allocation of significant resources, including managerial and financial, to a global health threat that is unpredictable and could rapidly dissipate or against which our vaccine, if developed, may not be partially or fully effective, and may ultimately prove unsuccessful or unprofitable. Furthermore, there are no assurances that our vaccine will be approved for inclusion in government stockpile programs, which may be material to the commercial success of the product candidate, either in the United States or abroad. Although we have a dedicated manufacturing facility, we do not have sufficient manufacturing infrastructure to support a global roll-out of mRNA-1273 on our own. For example, we are dependent on Lonza Ltd. to enable larger scale manufacture of mRNA-1273. As a result, we have formed a strategic collaboration with Lonza Ltd. and will need to form additional collaborations with third parties, including contract manufacturing organizations, government and non-government

organizations, and other funding and manufacturing sources to do so. We have not previously ramped our organization for a commercial launch of any product, and doing so in a pandemic environment with an urgent, critical global need creates additional challenges such as distribution channels, intellectual property disputes or challenges, and the need to establish teams of people with the relevant skills worldwide. We may also face challenges with sourcing a sufficient amount of raw materials to support the demand for a vaccine. We may be unable to effectively create a supply chain for mRNA-1273 that will adequately support demand. Furthermore, we will encounter significant additional capital requirements as we move through clinical studies of mRNA-1273 and toward a potential commercial launch. While our collaboration with BARDA will help us meet these capital requirements, additional investment, whether from our own capital resources or through collaborations with others, will be necessary. We cannot guarantee that any of these new challenges and requirements will be met in a timely manner or at all.” Bancel and Meline, *op. cit.*

¹²⁴ In the spring 2021 Moderna SEC filings, the company makes the following statements: “Although we have a dedicated manufacturing facility, we do not have sufficient manufacturing infrastructure to support a global roll-out of mRNA-1273 on our own. For example, we rely on Lonza Ltd. to enable larger scale manufacture of mRNA-1273. As a result, we have formed a strategic collaboration with Lonza Ltd. and will need to form additional collaborations with third parties, including contract manufacturing organizations, government and non-government organizations, and other funding and manufacturing sources to do so. We have formed a collaboration with Catalent, Inc. for large-scale, commercial fill-finish manufacturing of mRNA-1273, and a collaboration with Laboratorios Farmacéuticos Rovi, S.A., or ROVI, for large-scale, commercial fill-finish manufacturing of mRNA-1273 intended in principle to supply markets outside of the U.S. starting in early 2021 at ROVI’s facility in Madrid, Spain. We have not previously ramped our organization for a commercial launch of any product, and doing so in a pandemic environment with an urgent, critical global need creates additional challenges such as distribution channels, intellectual property disputes or challenges, and the need to establish teams of people with the relevant skills worldwide. We may also face challenges with sourcing a sufficient number of raw materials to support the demand for a vaccine. We may be unable to effectively create a supply chain for mRNA-1273 that will adequately support demand.” Bancel and Meline, *op. cit.*

¹²⁵ Bancel and Meline, *op. cit.* “For the first quarter of 2021, we delivered approximately 88 million doses of our COVID-19 vaccine to the U.S. government and approximately 14 million doses to other governments, and recognized \$1.7 billion in product sales.”

¹²⁶ In the company’s 2021 SEC filing, they make the following statement: “For the second quarter of 2021, we delivered approximately 126 million doses of our COVID-19 vaccine to the U.S. government

and approximately 73 million doses to other governments, and recognized \$4.2 billion in product sales.” Bancel and Meline, *op. cit.*

¹²⁷ Bancel and Meline, *op. cit.* “These investments are expected to facilitate a doubling of drug substance manufacturing from Lonza’s Switzerland-based facility, a more than doubling of formulation, fill and finish and drug substance manufacturing at Rovi’s Spain-based facility, as well as a 50% increase of drug substance at Moderna’s facilities in the U.S. When completed, the investments are expected to also result in an increase in safety stock of raw materials and finished product used to deliver committed volumes. These forecasted increases to our supply are subject in part to performance by our manufacturing partners, which will require ramping-up capabilities at their own facilities and the hiring of qualified manufacturing personnel.”

¹²⁸ In the company’s 2021 SEC filing, they make the following statement: “In the second quarter of 2021, we announced additional investments to facilitate the increased supply of our COVID-19 vaccine from our own and partnered manufacturing facilities, and an expansion of the Moderna Technology Center (MTC) in Norwood, Massachusetts, to more than double our facility space to help transform it from a production and lab space to an industrial technology center. As a result of these investments, we expect that we will supply between 800 million and 1 billion doses of our COVID-19 vaccine in 2021, at the 100 µg dose. We anticipate these investments will also increase our global 2022 capacity for the vaccine to up to 3 billion doses, in the event that our 2022 production is dedicated to 50 µg booster doses.” Bancel and Meline, *op. cit.*

¹²⁹ In the company’s spring 2020 SEC filings they make this illustrative statement: “The regulatory pathway for mRNA-1273 is continually evolving, and may result in unexpected or unforeseen challenges. To date, mRNA-1273 has moved rapidly through the FDA regulatory process. However, the speed at which all parties are moving to create, test and approve a vaccine for COVID-19 is highly unusual, and evolving or changing plans or priorities at the FDA, including based on new knowledge of COVID-19 and how the disease affects the human body, may significantly affect the regulatory pathway for mRNA-1273. Results from clinical testing may raise new questions and require us to redesign proposed clinical trials, including revising proposed endpoints or adding new clinical trial sites or cohorts of subjects. In addition, the FDA’s analysis of clinical data may differ from our interpretation and the FDA may require that we conduct additional analyses. The FDA has the authority to grant an Emergency Use Authorization to allow unapproved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions when there are no adequate, approved, and available alternatives. If we are granted an Emergency Use Authorization for mRNA-1273, we would be able to commercialize mRNA-1273 prior to FDA approval. Furthermore, the FDA may revoke an Emergency Use Authorization where it is determined that the underlying health emergency no longer exists or warrants such authorization, and we cannot predict how long, if ever, an Emergency Use Authorization would remain in place. Such revocation could adversely impact our business in a variety of ways, including if mRNA-1273 is not yet approved by the FDA and if we and our manufacturing partners have invested in the supply chain to provide mRNA-1273 under an Emergency Use Authorization.” Bancel and Kim, *op. cit.*

¹³⁰ Bancel and Meline, *op. cit.* “We have also received authorization for our COVID-19 vaccine from health agencies in more than 50 countries and from the World Health Organization. Additional authorizations are currently under review in other countries. In addition, we have received authorization for our COVID-19 vaccine for use in adolescents in the European Union and Japan and have pending applications for authorization to administer the vaccine to adolescents with regulatory agencies in the United States and other countries.”

¹³¹ Bancel and Meline, *op. cit.* “The final analysis of adjudicated cases from the Phase 3 clinical trial for mRNA-1273, which we refer to as the COVE Study, demonstrated efficacy of 93% through six months

after the second dose of the vaccine. The final analysis also demonstrated greater than 98% efficacy against severe cases of COVID-19 and 100% efficacy against death caused by COVID-19 in the per protocol cohort. The final analysis also demonstrated consistency in our subgroup analysis, including analyses by gender, by race and by preexisting medical conditions. The safety profile for mRNA-1273 continues to be consistent with the Phase 3 data over the longer period of safety follow up and across population subgroups.”

¹³² Bancel and Meline, *op. cit.* “On June 1, 2021, we initiated the rolling submission process with the U.S. FDA for a Biologics License Application for our COVID-19 vaccine and we currently anticipate completing our submission in August 2021.”

¹³³ Bancel and Meline, *op. cit.* “On December 18, 2020, we received an Emergency Use Authorization from the U.S. Food and Drug Administration (FDA) for the emergency use of the Moderna COVID-19 Vaccine... in individuals 18 years of age or older.”

¹³⁴ Bancel and Kim, *op. cit.* “On June 1, 2021, we initiated the rolling submission process with the U.S. FDA for a Biologics License Application for our COVID-19 vaccine and we currently anticipate completing our submission in August 2021.”

¹³⁵ In the company’s 2021 SEC filing, they make the following statement: “We have also received authorization for our COVID-19 vaccine from health agencies in more than 50 countries and from the World Health Organization. Additional authorizations are currently under review in other countries. In addition, we have received authorization for our COVID-19 vaccine for use in adolescents in the European Union and Japan and have pending applications for authorization to administer the vaccine to adolescents with regulatory agencies in the United States and other countries.” Bancel and Meline, *op. cit.*

¹³⁶ Bancel and Meline, *op. cit.* “The Conditional Marketing Authorization (CMA) for our COVID-19 vaccine in the European Union has been expanded to include adolescents 12 years of age and older. In addition, the Japanese Ministry of Health, Labor and Welfare also approved our COVID-19 vaccine for ages 12 to 17. We have filed for an EUA for adolescents with the U.S. FDA as well as with additional regulatory agencies around the world.”

¹³⁷ Weiland, Noah. “High Hopes for Johnson& Johnson’s COVID-19 Vaccine Have Fizzled in the U.S.” *New York Times*. Jul. 20, 2021. Web. Apr. 10, 2022.
<<https://www.nytimes.com/2021/06/18/us/politics/johnson-johnson-covid-vaccine.html>>.

¹³⁸ Kuchler and Abboud, *op. cit.*

¹³⁹ In the company’s spring 2021 SEC filing, they make the following statement: “The Company continues to evaluate and monitor both its internal and external supply arrangements, including its contract with Emergent BioSolutions and related production activities at its Bayview, Maryland facility. The Company has established a global vaccine supply network, where, in addition to its internal manufacturing site in Leiden, the Netherlands, ten other manufacturing sites will be involved in the production of vaccine across different countries and continents. The Company does not believe that a disruption at a vaccine manufacturing site, or the resulting delay would have a material financial impact on the Company’s consolidated financial statements or results.” Bancel and Meline, *op. cit.*

¹⁴⁰ See Loftus, Peter and Thomas M. Burton. “FDA Probes Cause of Failed Johnson& Johnson COVID-19 Vaccine Batch.” *The Wall Street Journal*. Apr. 1, 2021. Web. Apr. 10, 2022.
<<https://www.wsj.com/articles/fda-probes-cause-of-failed-johnson-johnson-COVID-19-vaccine-batch-11617319603>>; and Weiland, *op. cit.*

¹⁴¹ In Moderna’s spring 2021 SEC filing, they make the following statement: “In fiscal 2020, the Company entered into a series of contract manufacturing arrangements for vaccine production with third party contract manufacturing organizations. These arrangements provide the Company with future supplemental commercial capacity for vaccine production and potentially transferable rights to such production if capacity is not required. Amounts paid and contractually obligated to be paid to these contract manufacturing organizations of approximately \$1.0 billion are reflected in the prepaid expenses and other, other assets, accrued liabilities and other liabilities accounts in the Company’s consolidated balance sheet upon execution of each agreement.” Bancel and Meline, *op. cit.*

¹⁴² Bancel and Kim, *op. cit.*

¹⁴³ “...the Company has entered into certain vaccine development cost sharing arrangements with government related organizations.”

¹⁴⁴ Kirkegaard, *op. cit.*

¹⁴⁵ In the company’s spring 2021 SEC filing, they make the following statement: “The Company continues to evaluate and monitor both its internal and external supply arrangements, including its contract with Emergent BioSolutions and related production activities at its Bayview, Maryland facility. The Company has established a global vaccine supply network, where, in addition to its internal manufacturing site in Leiden, the Netherlands, ten other manufacturing sites will be involved in the production of vaccine across different countries and continents. The Company does not believe that a disruption at a vaccine manufacturing site, or the resulting delay would have a material financial impact on the Company’s consolidated financial statements or results.” Bancel and Meline, *op. cit.*

¹⁴⁶ See Loftus and Burton, *op. cit.*; and Weiland, *op. cit.*

¹⁴⁷ In Moderna’s spring 2021 SEC filing, they make the following statement: “In fiscal 2020, the Company entered into a series of contract manufacturing arrangements for vaccine production with third party contract manufacturing organizations. These arrangements provide the Company with future supplemental commercial capacity for vaccine production and potentially transferable rights to such production if capacity is not required. Amounts paid and contractually obligated to be paid to these contract manufacturing organizations of approximately \$1.0 billion are reflected in the prepaid expenses and other, other assets, accrued liabilities and other liabilities accounts in the Company’s consolidated balance sheet upon execution of each agreement.” Bancel and Meline, *op. cit.*

¹⁴⁸ See Loftus and Burton, *op. cit.*; Weiland, *op. cit.*; and Nettles, Richard. “Statement of Dr. Richard Nettles, M.D.” Johnson & Johnson. Feb. 23, 2021. p. 7. Web. Apr. 10, 2022. <**Error! Hyperlink reference not valid.**<https://docs.house.gov/meetings/IF/IF02/20210223/111226/HHRG-117-IF02-Wstate-NettlesR-20210223.PDF>>.

¹⁴⁹ Kenilworth, N. J. “Merck to Help Produce Johnson& Johnson’s COVID-19 Vaccine; BARDA to Provide Merck with Funding to Expand Merck’s Manufacturing Capacity for COVID-19 Vaccines and Medicines.” Merck. Mar. 2, 2021. Web. Apr. 10, 2022. <**Error! Hyperlink reference not valid.**<https://www.merck.com/news/merck-to-help-produce-johnson-BARDA-to-provide-merck-with-funding-to-expand-mercks-manufacturing-capacity-for-COVID-19-vaccines-and-medicines/>>.

¹⁵⁰ Burton, Thomas M. “FDA Authorizes More COVID-19 Vaccine Doses from Troubled Baltimore Plant.” *The Wall Street Journal*. Jun. 15, 2021. Web. Apr. 10, 2022. <<https://www.wsj.com/articles/fda-authorizes-15-million-additional-COVID-19-vaccine-doses-from-troubled-baltimore-plant-11623803290>>: “The federal government worked with AstraZeneca to move production of its vaccine out of the plant so it could focus exclusively on making J&J’s vaccine, the person familiar with the matter

said.”

¹⁵¹ Jerving, Sara. “Deal to Send COVID-19 Vaccines from South Africa to Europe Dismantled.” DEVEX. Sept. 2, 2021. Web. Apr. 10, 2022. <<https://www.devex.com/news/deal-to-send-COVID-19-vaccines-from-south-africa-to-europe-dismantled-101532>>.

¹⁵² Reuters. “India Approves Johnson & Johnson Covid Vaccine for Emergency Use.” *The Guardian*. Aug. 7, 2021. Web. Apr. 10, 2022. <<https://www.theguardian.com/world/2021/aug/07/india-approves-johnson-johnson-covid-vaccine-for-emergency-use>>.

¹⁵³ Loftus and Burton, *op. cit.*

¹⁵⁴ Rizvi, “Leading COVID-19 Vaccine Candidates depend on NIH Technology.”

¹⁵⁵ “Certain of our technologies, including in particular certain proprietary manufacturing processes or technologies and/or neoantigen prediction technologies, are protected as trade secrets.” BioNtech SE, SEC Filing, July 21, 2020.

¹⁵⁶ Sampat, Bhaven N. and Kenneth C. Shadlen. “The COVID-19 Innovation System.” *Health Affairs* 40.3 (2021): pp. 400–409. <<https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2020.02097>>.

¹⁵⁷ Wouters, Olivier J., Kenneth C. Shadlen, Maximilian Salcher-Konrad, Andrew J. Pollard, Heidi J. Larson, Yot Teerawattananon and Mark Jit. “Challenges in Ensuring Global Access to COVID-19 Vaccines: Production, Affordability, Allocation, and Deployment.” *Lancet* 397.10278 (2021): pp. 13–19.

¹⁵⁸ Kirkegaard, *op. cit.*

¹⁵⁹ Franklin-Wall, Oliver. “An Oral History of Oxford/AstraZeneca: ‘Making a vaccine in a year is like landing a human on the moon’.” *The Guardian*. Aug. 28, 2021. Web. Apr. 12, 2022. <<https://www.theguardian.com/society/2021/aug/28/oral-history-of-oxfordastrazeneca-making-a-vaccine-in-a-year-is-like-landing-a-human-on-the-moon>>: “Cath Green, head of the clinical biomanufacturing facility Sarah [Gilbert] had already made a vaccine against MERS, so she knew what the vaccine against the new coronavirus was going to look like. They take the DNA sequence of the coronavirus spike protein from the Chinese lab and adapt that to make it the right fit to go into our system. The Jenner lab take that sequence and insert it into a bigger sequence which contains the adenovirus genome. So I received from them a really small tube with a few micrograms of DNA. My job was to make that into the vaccine.”

¹⁶⁰ *Ibid.* “On 11 January 2020, media reported the first death from what would come to be known as SARS-CoV-2, or COVID-19. The same day, Chinese virologist Zhang Yongzhen published the genome sequence of the virus online. Lambe received the genome in her email inbox early Saturday morning.

Lambe [associate professor, Jenner Institute] We knew it was coming, and we’d already had a discussion about what to do. We designed [the vaccine] over that weekend.”

“Sarah Gilbert, Saïd professor of vaccinology, Jenner Institute [Before COVID] I was developing vaccines against a range of emerging pathogens, specifically MERS, Nipah and Lassa [virus]. We also had applied for funding to work on preparedness for “disease X” – the unknown pathogen that is coming. But it wasn’t funded, so we didn’t manage to put any of those plans in place.”

“Gilbert We knew before the genome came that it was a new coronavirus, not the original SARS, not MERS or any of the seasonal human coronaviruses. But because it *was* a coronavirus, we knew the part of the genome we needed was the part that encodes the spike protein on the surface. That’s what you want to raise an antibody response against.”

¹⁶¹ Although the details are incomplete, according to various sources, in May 2020, Oxford Biomedica signed up to produce the vaccine for clinical trials; in June 2020, a Scottish plant (run by Symbiosis Biopharmaceuticals) agreed to do the fill-and-finish work.

¹⁶² “How AstraZeneca’s Vaccine Was Hit by Flawed Trials, Defects and Politics – But Might Still Save the World.” *Financial Times*. Feb. 5, 2021. Web. Apr. 10, 2022. <<https://www.ft.com/content/d0fd6c4c-939a-43c7-a9b9-47c8d3cab253>>: “Even before selecting their partner in April, the university scientists had made a head start — but took a route that would cause trouble later. The scientists decided not to test the vaccine among large groups of over-65s, until they had plenty of evidence that it was safe in younger people. Andrew Pollard, director of the Oxford Vaccine Group, told the FT the decision was ‘cautious — and at the time, that was right’. Almost a year later, however, the lack of data has led to many European countries advising against its use on older people. Emmanuel Macron, president of France, went further, saying — without producing evidence — that ‘everything points to thinking it is quasi-ineffective on people older than 65, some say those 60 years or older’.”

¹⁶³ AstraZeneca PLC, “H1 2021 Results.” Jul. 29, 2021. Web. Apr. 10, 2022. <https://www.astrazeneca.com/content/dam/az/PDF/2021/h1-2021/H1_2021_results_announcement.pdf>, p. 39.

¹⁶⁴ Strasburg, Jenny. “AstraZeneca COVID-19 Antibody Treatment Suffers Setback.” *The Wall Street Journal*. Jun. 15, 2021. Web. Apr. 10, 2022. <<https://www.wsj.com/articles/astrazeneca-COVID-19-antibody-treatment-suffers-setback-11623755934>>.

¹⁶⁵ AstraZeneca PLC, *op. cit.*, 40.

¹⁶⁶ Franklin-Wall, *op. cit.*

¹⁶⁷ “How AstraZeneca’s Vaccine Was Hit by Flawed Trials, Defects and Politics.”

¹⁶⁸ The Editorial Board. “A Vaccine Progress Report.” *The Wall Street Journal*. Jun. 22, 2020. Web. Apr. 10, 2022. <<https://www.wsj.com/articles/a-vaccine-progress-report-11595461075>>: “AstraZeneca Executive Vice President Mene Pangalos explained that it is having ‘unprecedented’ interactions with regulators around-the-clock, and regulators in other countries are also reviewing its data.”

¹⁶⁹ Walker, Joseph and Jenny Stausburg. “AstraZeneca Defends Dosing Error in COVID-19 Vaccine Trial.” *The Wall Street Journal*. Nov. 25, 2020. Web. Apr. 10, 2022. <<https://www.wsj.com/articles/astrazeneca-defends-dosing-error-in-COVID-19-vaccine-trial-11606358805>>: “A top executive at AstraZeneca AZN +0.81% PLC pushed back on Wednesday against criticism that the company failed to disclose enough data from a clinical trial of its COVID-19 vaccine earlier this week, and acknowledged skepticism about the vaccine’s 90% effectiveness in a group of patients who were accidentally given a lower dose than intended. ‘I’m not going to pretend it’s not an interesting result, because it is—but I definitely don’t understand it and I don’t think any of us do,’ said Mene Pangalos, AstraZeneca’s executive vice president for biopharmaceuticals research and development. ‘It was surprising to us.’ The U.K. company said on Monday that the vaccine it is codeveloping with the University of Oxford was on average about 90% effective in preventing COVID-19 when volunteers were given a half-dose shot followed by a full dose a month or more later, but only 62% effective when two full doses were given. The data pooled trial results from the U.K. and Brazil. AstraZeneca on Monday said in interviews with news media that the half-dose regimen was the result of a manufacturing error, which neither the company nor Oxford initially mentioned in their press releases announcing the results.”

¹⁷⁰ Strasburg, “AstraZeneca COVID-19 Antibody Treatment Suffers Setback.”

¹⁷¹ The PIIIE report states “On September 9, 2020, AstraZeneca paused all of its trials after a patient in its U.K. Phase 3 trial experienced an unexplained illness. Its U.K. trial resumed mid-September 2020. Soon thereafter, trials began again in Brazil, South Africa, India, and Japan. Only in late October 2020 did the FDA authorize resumption of the U.S. Phase 3 trial. This delay has been suggested to be a public sign of discord with U.S. regulators. On November 23, AstraZeneca released what it believed were positive results from two dosing regimens, with pooled data from different phases of trials taking place in different countries. The results, ultimately published in *The Lancet* on December 8, confused and sowed doubts among some regulators, especially in the U.S. The U.S. National Institute for Allergy and Infectious Diseases (NIAID), part of the NIH, indicated that the trial’s independent data-monitoring board had raised ‘concerns’ about the data AstraZeneca had chosen to highlight.”

¹⁷² Bancel and Meline, *op. cit.*

¹⁷³ “U.S. regulators have set the bar for authorizing vaccines at 50% effectiveness, but vaccines in development by Moderna Inc., and partners Pfizer Inc. and Germany’s BioNTech SE have set the benchmark even higher with study results showing greater than 90% effectiveness. Those vaccines use a new gene-based technology that, despite its impressive clinical results thus far, requires the shots to be stored at subzero temperatures. AstraZeneca’s vaccine can be stored in a more standard refrigerator, which could make it attractive to low- and middle-income nations.”

¹⁷⁴ Weiland, *op. cit.*

¹⁷⁵ AstraZeneca PLC, *op. cit.*, p. 4.

¹⁷⁶ Callaway, *op. cit.*

¹⁷⁷ AstraZeneca. “Innovating Production and Manufacture to Meet the Challenge of COVID-19.” Jan. 2021. Web. Apr. 10, 2022. <<https://www.astrazeneca.com/what-science-can-do/topics/technologies/innovating-production-and-manufacture-to-meet-the-challenge-of-covid-19.html>>.

¹⁷⁸ AstraZeneca PLC, *op. cit.*, p. 56.

¹⁷⁹ “How AstraZeneca’s Vaccine Was Hit by Flawed Trials, Defects and Politics”: “*As the world stood still in lockdown in April 2020, a group of Oxford researchers packed the cell cultures needed to make their experimental coronavirus vaccine and quietly shipped them to India’s Serum Institute. The scientists were worried that the university’s prospective partner, AstraZeneca, eager to control the intellectual property behind the shot, would stop them, and that their vaccine would never reach the poorer nations that most needed it, according to three people with knowledge of the matter. In the case of AstraZeneca, their fears would prove to be unfounded. Oxford and the Anglo-Swedish drugmaker have since signed a licensing deal with the Serum Institute. In hindsight, the covert shipment, intended to guarantee the mass production of COVID-19 shots at low costs, was an opening salvo.*”

¹⁸⁰ “How AstraZeneca’s Vaccine Was Hit by Flawed Trials, Defects and Politics”: “The unorthodox data that shook some experts’ confidence came after early manufacturing fumbles. Oxford was working with a contract manufacturer, which ended up making a half dose by accident. Then, when the scientists decided to test a two-dose course, they were hit by production delays, which meant a longer gap between doses as they waited for supplies. According to Oxford’s Pollard, this mistake has proved to be a blessing. ‘At that time, it felt like a frustration, but in retrospect it turned out to be extremely useful,’ he said. Later analysis showed it was probably the longer interval that made the vaccine more effective. This finding helped assure regulators that spacing out the two doses, as the UK has, would allow more people to be vaccinated with the bonus of added efficacy.”

¹⁸¹ Strasburg, “AstraZeneca COVID-19 Antibody Treatment Suffers Setback.”

¹⁸² AstraZeneca PLC, *op. cit.*, p. 55.

¹⁸³ As the vaccine began to be rolled out, a handful of Europeans experienced a rare blood-clotting condition, which led to a few deaths. Many countries—including France, Germany, Italy, Portugal and Spain—paused their vaccination campaigns while the EMA investigated the source of the side effects. Some countries eventually resumed distributing the vaccine, but some discontinued its use entirely.

¹⁸⁴ Loftus and Burton, *op. cit.*

¹⁸⁵ Truesdell, Richard D., Paul Van der Bill and Nathan Aijashvili. “Form F-1 Registration Statement under the Securities Act of 1933, CureVac N.V.” United States Securities and Exchange Commission. Washington, DC. 20549. Jan. 25, 2021. Web. Apr. 10, 2022. <<https://curevac.gcs-web.com/node/6356/html>>.

¹⁸⁶ Zimmer, Carl. “This New COVID-19 Vaccine Could Bring Hope to the Unvaccinated World.” *The New York Times*. May 5, 2021. Web. Apr. 10, 2022. <<https://www.nytimes.com/2021/05/05/health/covid-vaccine-curevac.html>>: “For CureVac’s co-founder, the biologist Ingmar Hoerr, the company’s COVID-19 vaccine trial is the culmination of a quarter-century’s worth of work with RNA, a molecule that helps turn DNA into the proteins that do the work of our cells. For years, CureVac and other RNA vaccine companies toiled on perfecting their vaccines. CureVac’s first attempt at a rabies vaccine demonstrated it was safe, but it yielded a weak response from the immune system. The company has since retooled that vaccine, and the updated version has shown promise in early clinical studies. But other efforts ended in failure. In 2017, CureVac announced that its RNA vaccine against prostate cancer offered no benefits to patients.”

¹⁸⁷ Zimmer, *op. cit.*: “C.E.P.I. gave \$34 million to CureVac in 2019 to support its development of RNA vaccines for future pandemics. CureVac lagged behind. C.E.P.I. provided the company with \$15 million, but CureVac would require far more. ‘If you do this, you need a considerable amount of cash,’ Franz-Werner Haas, the chief executive of CureVac, said in an interview. ‘And the considerable amount of cash was not there’.”

¹⁸⁸ CureVac. “CureVac Establishes European-based Network to Ramp up Manufacturing of Its COVID-19 Vaccine Candidate, CVnCoV.” Nov. 17, 2020. Web. <<https://www.curevac.com/en/2020/11/17/curevac-establishes-european-based-network-to-ramp-up-manufacturing-of-its-COVID-19-vaccine-candidate-cvnCoV/>>: in December 2020, “CureVac is building an integrated European vaccine manufacturing network with several Contract Development and Manufacturing Organization (CDMO) partners. With this strategy, the company will significantly increase CureVac’s existing manufacturing capacity, allowing CureVac to develop up to several hundred million doses of its vaccines per year and to manage potential supply chain risks by working with partners during each of the key steps in the manufacturing process.”

¹⁸⁹ CureVac. “CureVac and Fareva Sign Agreement for Fill & Finish Manufacturing of CureVac’s COVID-19 Vaccine Candidate, CVnCoV.” Joint press release. Dec. 9, 2020. Web. <<https://www.curevac.com/en/2020/12/09/curevac-and-fareva-sign-agreement-for-fill-finish-manufacturing-of-curevacs-COVID-19-vaccine-candidate-cvnCoV-joint-press-release/>>: “In December 2020, Curevac and Fareva announced an agreement regarding the fill & finish manufacturing of CureVac’s COVID-19 vaccine candidate, CVnCoV, at Fareva’s Pau and Val-de-Reuil-sites in France. ‘We are proud to contribute to the fill & finish manufacturing of this innovative vaccine candidate from CureVac. This agreement confirms Fareva’s strategy of investing significantly in the areas of sterile manufacturing, enlarging our technology offering,’ said Alexandre Bastit, Vice President of EMEA

Pharma Sales at Fareva. ‘We are pleased to partner with Fareva for the fill & finish manufacturing of our COVID-19 vaccine candidate in France,’ added Dr. Florian von der Mülbe, Chief Production Officer of CureVac. ‘Fareva is an experienced and reliable partner that will help to increase the overall production capacity for our vaccine, and by partly manufacturing our vaccine in France, we will hopefully be in a position to contribute to the protection of French citizens against the virus’.”

¹⁹⁰ Kuchler and Abboud, *op. cit.*: “GSK, which had previously partnered with German biotech CureVac, announced last week it will extend the partnership to include CureVac’s COVID-19 jab. The UK drugmaker will help with manufacturing of the mRNA vaccine and the two will work together to develop a vaccine to target many strains of the virus at once, projected to arrive in 2022. It hopes to be a ‘fast follower’, Breuer said. ‘At the start of the pandemic, mRNA was unproven and GSK’s own mRNA platform was not as prepared as some of the specialist players to move immediately,’ he said. ‘When variants started to emerge and it became clearer that existing vaccine efficacy declined for some variants, we felt GSK could play a leading role in the development of next generation vaccines’.”

¹⁹¹ “GSK today announced the publication of preclinical data investigating immune responses as well as the protective efficacy of CureVac’s first-generation vaccine candidate, CVnCoV, and second-generation vaccine candidate, CV2CoV, against SARS-CoV-2 challenge in non-human primates. The study, conducted in collaboration with Dan Barouch, MD, PhD, of Beth Israel Deaconess Medical Center, assessed cynomolgus macaques vaccinated with 12µg of either the first or second-generation vaccine candidate. Better activation of innate and adaptive immune responses was achieved with CV2CoV, resulting in faster response onset, higher titers of antibodies and stronger memory B and T cell activation as compared to the first-generation candidate, CVnCoV. Higher antibody neutralizing capacity was observed with CV2CoV across all selected variants, including the Beta, Delta and Lambda variants. During challenge with the original SARS-CoV-2 virus, animals vaccinated with CV2CoV were found to be better protected based on highly effective clearance of the virus in the lungs and nasal passages. The full manuscript of the preclinical data is available on the preprint server bioRxiv. ‘In this animal model, CV2CoV is shown to induce broad antibody and cellular immune responses very similar to the breadth of the immune responses observed after infection with SARS-CoV-2,’ said Dr. Igor Splawski, Chief Scientific Officer of CureVac. ‘The current study shows that the immune responses and resulting protection produced by our second-generation candidate, based on our mRNA technology featuring targeted optimizations, are substantially improved in non-human primates against both the original SARS-CoV-2 virus as well as the Beta and Delta Variants of Concern and the Lambda Variant of Interest.’ Dr. Rino Rappuoli, Chief Scientist and head of GSK Vaccines R&D said: ‘The mRNA technology is a key strategic priority for us, and we are investing significantly in a number of mRNA programs focused on the collaboration with CureVac. The strong immune response and protection in preclinical testing of this second-generation mRNA backbone are very encouraging and represent an important milestone for its further development.’ Within the study, CVnCoV and CV2CoV were tested in cynomolgus macaques immunized with a 12µg dose of the respective candidate on day 0 and day 28.”

¹⁹² CureVac. “CureVac’s COVID-19 Vaccine Candidate, CVnCoV, Demonstrates Protection Against SARS-CoV-2 B.1.351 Variant (South African Variant) in Preclinical Challenge Study.” Mar. 23, 2021. Web. <<https://www.curevac.com/en/2021/03/23/curevacs-COVID-19-vaccine-candidate-cvncov-demonstrates-protection-against-sars-cov-2-b-1-351-variant-south-african-variant-in-preclinical-challenge-study/>>: “CVnCoV, protects against challenge infections with the SARS-CoV-2 Variant of Concern B.1.351 (also referred to as the ‘South African’ variant) and a strain of the original SARS-CoV-2 B1 lineage (BavPat1) in a transgenic mouse model. Consistent with available variant studies, the neutralization capacity of robust antibody titers was shown to be impacted by the B.1.351 variant compared to the original strain. However, vaccinated animals were fully protected from lethal challenge infections with both strains. ‘Emergence of new SARS-CoV-2 strains, which exhibit the potential to escape an existing SARS-CoV-2 immunity, pose an increasing risk to the progress of current global

immunization efforts,’ said Igor Splawski, Ph.D., Chief Scientific Officer of CureVac. ‘To our knowledge, this is the first challenge study in a human ACE2 transgenic mouse model of severe disease that shows complete protection against one of the most threatening virus variants’.”

¹⁹³ August 2020: “An additional large-scale production facility supported by the European Investment Bank (EIB) at CureVac’s headquarters in Tübingen is currently in development.” CureVac. “CureVac and European Commission in Advanced Discussions to Supply up to 405 Million Doses of Potential mRNA-based COVID-19 Vaccine.” Aug. 20, 2020. Web. <<https://www.curevac.com/en/2020/08/20/curevac-and-european-commission-in-advanced-discussions-to-supply-up-to-405-million-doses-of-potential-mrna-based-covid-19-vaccine/>>.

¹⁹⁴ “Curevac and the European Commission have concluded exploratory talks outlining an Advanced Purchase Agreement (APA) for our potential mRNA-based COVID-19 vaccine. The envisaged contract with the European Commission is intended to provide all EU Member States with up to 225 million doses and an option for an additional purchase of 180 million doses, to be supplied once our mRNA-based vaccine has proven to be safe and effective against COVID-19.” CureVac, “CureVac and European Commission in Advanced Discussions.”

¹⁹⁵ CureVac, “CureVac Establishes European-based Network.”

¹⁹⁶ CureVac, “CureVac and Fareva Sign Agreement.”

¹⁹⁷ Zimmer, *op. cit.*

¹⁹⁸ TipRanks. “Novavax’s COVID-19 Vaccine Candidate Could Be the One, Says Top Analyst.” Yahoo!. May 21, 2020. Web. Apr. 10, 2022. <<https://finance.yahoo.com/news/novavax-covid-19-vaccine-candidate-001437548.html>>.

¹⁹⁹ See Findlay, Stephanie and Anna Gross. “Not Enough Covid Vaccine for All Until 2024, Says Biggest Producer.” *The Financial Times*. Sept. 13, 2020. Web. Apr. 10, 2022. <<https://www.ft.com/content/a832d5d7-4a7f-42cc-850d-8757f19c3b6b>>.

²⁰⁰ Carlson, Robert and Holly Lutmer. “Japan Drops Moderna for Un-authorized COVID-19 Vaccine.” Precision Vaccination. Sept. 9, 2021. Web. Apr. 10, 2022. <<https://www.precisionvaccinations.com/2021/09/09/japan-drops-moderna-un-authorized-covid-19-vaccine>>.

²⁰¹ See “Novavax Launches Late-Stage Covid Vaccine Trial in US.” *The Financial Times*. Dec. 28, 2020. Web. Apr. 10, 2022. <<https://www.ft.com/content/2dffdd47-4d0c-48cc-a729-8f33709c259d>>: “Novavax’s vaccine is stable at between 2 and 8C, and so does not require the special ultra-cold chain for transportation and distribution needed by BioNTech/Pfizer’s jab.”

²⁰² CBS Baltimore. “Novavax Receives Additional Funding for COVID-19 Vaccine Candidate.” *13 WJZ*., May 12, 2020. Web. Apr. 10, 2022. <<https://baltimore.cbslocal.com/2020/05/12/novavax-coronavirus-vaccine-candidate-funding-latest/>>.

²⁰³ Rees, Victoria. “CEPI Invests \$384m in Novavax COVID-19 Vaccine Candidate.” *European Pharmaceutical Review*. May 12, 2020. Web. Apr. 10, 2022. <<https://www.europeanpharmaceuticalreview.com/news/119321/cepi-invests-384m-in-novavax-covid-19-vaccine-candidate/>>: “The Coalition for Epidemic Preparedness Innovations (CEPI) will provide Novavax with up to \$384 million in additional funding toward clinical development and large-scale manufacturing of the company’s COVID-19 vaccine candidate NVX-CoV2373, CEPI and the

company said. The funding multiplies CEPI's investment in NVX-CoV2373, which began with a \$4 million award in March. Novavax's total \$388 million in CEPI funding accounts for 87% of the total \$446 million awarded by the Coalition toward COVID-19 vaccine R&D."

²⁰⁴ Thomas, Katie. "U.S. Will Pay \$1.6 Billion to Novavax for Coronavirus Vaccine." *The New York Times*. Jul. 7, 2020. Web. Apr. 10, 2022. <<https://www.nytimes.com/2020/07/07/health/novavax-coronavirus-vaccine-warp-speed.html>>.

²⁰⁵ Callaway, *op. cit.*

²⁰⁶ See "Novavax Launches Late-Stage Covid Vaccine Trial in US": "Novavax is launching a late-stage trial of its COVID-19 vaccine in the US and Mexico, fueled by an award of up to \$1.6bn from Operation Warp Speed. The Maryland-based biotech company kicks off the trial at 115 sites on Monday, aiming to recruit up to 30,000 participants. Two-thirds will receive the vaccine, with the remaining one-third taking a placebo."

²⁰⁷ Reuters Staff. "Novavax Expects Delayed U.S. COVID-19 Vaccine Trial to Start in Coming Weeks." Reuters. Nov. 20, 2020. Web. Apr. 10, 2022. <**Error! Hyperlink reference not valid.**<https://www.reuters.com/article/us-health-coronavirus-novavax-vaccine/novavax-expects-delayed-u-s-covid-19-vaccine-trial-to-start-in-coming-weeks-idUSKBN28A1E1>>.

²⁰⁸ LaFraniere, Sharon. "Novavax Says U.S. Will Pause Funding for Production of Its Vaccine." *The New York Times*. Aug. 8, 2020. Web. Apr. 10, 2022. <<https://www.nytimes.com/2021/08/06/us/politics/novavax-coronavirus-vaccine.html>>: "Novavax, the Maryland firm that won a \$1.75 billion federal contract to develop and produce a coronavirus vaccine, said on Thursday that the federal government would not fund further production of its vaccine until the company resolves concerns of federal regulators about its work. The firm's disclosure came in a quarterly filing with the Securities and Exchange Commission. The Trump administration agreed to buy 110 million doses of vaccine from Novavax as part of its crash vaccine development program. Although the company reported in June that its vaccine had an efficacy of 90 percent against symptomatic COVID-19 cases, and 100 percent against severe disease, Novavax has struggled for months to mass manufacture its product. Its vaccine has not been authorized for distribution in the United States, and federal officials said it is unclear when or if it will be. Four people familiar with Novavax's operation said the company had been unable so far to demonstrate that its production process met Food and Drug Administration standards. Novavax said in a statement that the federal government continued to fund other work it had underway, including clinical trials. 'We do not expect any impact on our funding arrangement with the U.S. government to support overall development and production of 110 million doses of our vaccine candidate,' the firm said. The company's manufacturing problems come on top of production failures at a federally funded vaccine-making factory in Baltimore operated by Emergent BioSolutions. Federal regulators halted production at that plant for more than three months this year until the firm resolved quality control problems, including failure to prevent contamination that ruined tens of millions of doses. The plant had produced Johnson & Johnson's and AstraZeneca's vaccines but now manufactures doses only for Johnson & Johnson."

²⁰⁹ Bancel and Kim, *op. cit.*

²¹⁰ Hopkins, Jared S. "Merck Scraps COVID-19 Vaccine Candidates." *The Wall Street Journal*. Jan. 25, 2021. Web. Apr. 10, 2022. <<https://www.wsj.com/amp/articles/merck-scraps-covid-19-vaccine-candidates-11611575103>>.

²¹¹ Zuckerman, Gregory and Jared S. Hopkins. "Why Merck Is Playing Catchis in the Coronavirus Vaccine Chase." *The Wall Street Journal*. Oct. 23, 2020. Web. Apr. 10, 2022.

<<https://www.wsj.com/articles/why-merck-is-playing-catch-up-in-the-coronavirus-vaccine-chase-11603470832>>.

²¹² Kuchler and Abboud, *op. cit.*

²¹³ Strasburg, Jenny and Stu Woo. “Oxford Developed COVID-19 Vaccine, then Scholars Clashed over Money.” *The Wall Street Journal*. Oct. 21, 2020. Web. Apr. 10, 2022. <<https://www.wsj.com/articles/oxford-developed-covid-vaccine-then-scholars-clashed-over-money-11603300412>>.

²¹⁴ Bancel and Kim, *op. cit.*

²¹⁵ Bancel and Kim, *op. cit.*

²¹⁶ LaFraniere, Sharon, Sheryl Gay Stolberg, Michael D. Shear and Noah Weiland. “COVID-19: Biden Says Vaccine Doses Could Be Available for All Adult Americans by End of May.” *The New York Times*. Jul. 8, 2021. Web. Apr. 10, 2022. <<https://www.nytimes.com/live/2021/03/02/world/covid-19-coronavirus>>.

²¹⁷ Abboud, Leila. “Merck Abandons Bid to Develop COVID-19 Vaccine.” *The Financial Times*. Jan. 25, 2021. Web. Apr. 10, 2022. <<https://www.ft.com/content/6a0a7d49-4557-45bc-afd1-54a2ca7413fe>>.

²¹⁸ Sanofi. “Sanofi and GSK to Join Forces in Unprecedented Vaccine Collaboration to Fight COVID-19.” Sanofi.com. Apr. 14, 2020. Web. Apr. 10, 2022. <<https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-14-13-00-00>>.

²¹⁹ Strasburg, Jenny. “Sanofi-GSK COVID-19 Vaccine Set for Large-Scale Trials after Positive Results.” *The Wall Street Journal*. May 17, 2021. Web. Apr. 10, 2022. <<https://www.wsj.com/articles/sanofi-gsk-covid-19-vaccine-set-for-large-scale-trials-after-positive-results-11621252866>>.

²²⁰ Wu, Katherine J. “Sanofi Accelerates Its Timeline for Coronavirus Vaccine Development.” *The New York Times*. Jun. 23, 2020. Web. Apr. 10, 2022. <<https://www.nytimes.com/2020/06/23/health/sanofi-coronavirus-vaccine.html>>.

²²¹ Kuchler, Hannah. “Sanofi to Buy Partner Translate Bio for \$3.2bn IN MRNA Push.” *Financial Times*. Aug. 3, 2021. Web. Apr. 12, 2022. <<https://www.ft.com/content/26ddc089-eba3-4b99-9ab6-52ca3b81a2ba>>.

²²² Abboud, Leila. “Sanofi to Start Human Trials of MRNA Vaccine Against COVID-19.” *Financial Times*. Mar. 12, 2021. Web. Apr. 12, 2022. <<https://www.ft.com/content/df2c23a6-d610-4222-97aa-1bcd91773091>>.

²²³ Walker, Joseph. “Sanofi, GlaxoSmithKline Ink Coronavirus Vaccine Deal with U.S.” *The Wall Street Journal*. Jul. 31, 2020. Web. Apr. 12, 2022. <<https://www.wsj.com/articles/sanofi-glaxosmithkline-ink-coronavirus-vaccine-deal-with-u-s-11596193203>>.

²²⁴ Robbins, Rebecca. “A Vaccine from Sanofi and GSK Is Said to Produce Strong Immune Responses in a Midstage Study.” *The New York Times*. May 17, 2021. Web. Apr. 12, 2022. <<https://www.nytimes.com/2021/05/17/business/sanofi-glaxosmithkline-vaccine-trial.html>>.

²²⁵ Zimmer, Carl, Jonathan Corum, Sui-Lee Wee and Matthew Kristoffersen. “Coronavirus Vaccine Tracker.” *The New York Times*. Jun. 10, 2020. Web. Apr. 12, 2022. <<https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>>.

²²⁶ “Sanofi/Translate Bio: Do Recruit the Messenger.” *Financial Times*. Aug. 3, 2021. Web. Apr. 12, 2022. <<https://www.ft.com/content/76876e0a-4f49-4f2a-bb25-47010eacb0b8>>.

²²⁷ Strasburg, “Sanofi-GSK COVID-19 Vaccine Set for Large-Scale Trials.”

²²⁸ Dalton, Matthew and Joseph Walker. “Sanofi-GSK COVID-19 Vaccine Is Set Back by Lab Mistake.” *The Wall Street Journal*. Dec. 11, 2020. Web. Apr. 12, 2022. <<https://www.wsj.com/articles/broader-vaccine-plan-in-west-dealt-setback-by-sanofi-gsk-delay-11607696740>>.

²²⁹ Steinhauser, Gabriele, Drew Hinshaw and Betsy McKay. “Why a Grand Plan to Vaccinate the World against COVID-19 Unraveled.” *The Wall Street Journal*. May 26, 2021. Web. Apr. 12, 2022. <<https://www.wsj.com/articles/why-a-grand-plan-to-vaccinate-the-world-against-covid-unraveled-covax-11622045728>>.

²³⁰ Frank, Dach and Lurie, *op. cit.*

²³¹ *Ibid.*

²³² Bown and Bollyky, *op. cit.*

²³³ *Ibid.*

²³⁴ Williams, Heidi L. “Intellectual property rights and innovation: Evidence from the human genome”, *Journal of Political Economy*, 121 (1) (2013): pp.1–27.

²³⁵ Cunningham, Colleen, Ederer, Florian and Ma, Song. “Killer acquisitions”, *Journal of Political Economy*, 129 (3): pp. 649 – 702.

²³⁶ Jackson, Nick. “Why We Need a ‘portfolio approach’ to COVID-19 Vaccine Development.” *Gavi*. Sept. 28, 2020. Web. Apr. 12, 2022. <https://cepi.net/news_cepi/why-we-need-a-portfolio-approach-to-COVID-19-vaccine-development>.

Tables: The Determinants of COVID-19 Vaccine Success

Table 1: COVID-19 Vaccines: Selected Successes and Abandoned Candidates

<i>Vaccine Sponsor for Regulatory Approval or Authorization</i>	<i>Vaccine name</i>	<i>Authorized or approved to date in at minimum one OECD country?</i>	<i>Originating countries</i>	<i>Details of availability*</i>	<i>Number of country authorizations and approvals as of January 2022*</i>	<i>Vaccine platform</i>	<i>Selected for Case Study</i>
Astrazeneca/Oxford	Vaxzevria	yes	UK	Approved in Brazil. Emergency use in UK, EU, other countries	96	non-mRNA based	yes
Pfizer/BioNtech	Comirnaty	yes	Germany	Approved in US, other countries. Emergency use in EU, other countries	105	mRNA based	yes
NIH/Moderna	Spikevax	yes	US	Approved in Switzerland. Emergency use in US, EU, other countries	69	mRNA based	yes
Janssen		yes	US	Emergency use in US, EU, other countries	79	non-mRNA based	yes
Sinovac	CoronaVac	yes	China	Approved in China. Emergency use in other countries	38	non-mRNA based	no
Sinopharm	BIBP vaccine	yes	China	Approved in China, UAE, Bahrain. Emergency use in other countries	63	non-mRNA based	no
Gamaleya	Sputnik V	yes	Russia	Emergency use in Russia, other countries	74	non-mRNA based	no
Merck/Pasteur/iavi		abandoned	US			non-mRNA based	yes
Sanofi/Translate Bio		abandoned	France			mRNA based	yes
GSK		abandoned	UK			non-mRNA based	no
Curevac	CV2CoV	expected 2022	Germany			mRNA based	yes
Novavax	Nuvaxovid	yes	US	Approved in EU, other countries	29	non-mRNA based	yes
Inovio	INO-4800	in Phase III clinical trials	US			non-mRNA based	no
Bharat Biotech/BBIL	Covaxin	yes	India	India, Iran, Mexico, Zimbabwe, Ethiopia, Brazil, Botswana, Bahrain, other countries	16	non-mRNA based	no
Can Sino	Convidecia	yes	China	China, Mexico, Argentina, Chile, Ecuador, Hungary, Indonesia, Malaysia, Pakistan	9	non-mRNA based	no
Imperial College London/Morningside		abandoned	UK			non-mRNA based	no
Vector Institute	EpiVacCorona	yes	Russia	Russia, Turkmenistan, Venezuela	3	non-mRNA based	no

Legend: Vaccine authorized or approval status last assessed as of December 31, 2021.** To select case studies, I reviewed the international registry of clinical trials and clinicaltrials.gov to identify COVID-19 vaccine candidates in development since the inception of the epidemic in January 2020. Other data sources that were useful in conducting this review were COVID-19 vaccine trackers, available through various public sources and the peer-review literature, and various preprint services. I selected case study candidates to profile here based on the following criteria: (1) vaccines authorized or approved to date by at least one country's regulator, (2) a group of vaccine candidates that were abandoned in some phase of development or manufacturing by their sponsors to date, (3) and a group of vaccine candidates that are still in development. I took care to choose among candidates based on different vaccine platforms and those originating in various countries and regions of origin.

* Data from UNICEF, available at: <https://www.unicef.org/supply/covid-19-vaccine-market-dashboard>

**Authorized or approved is defined by UNICEF to be inclusive of country specific approval, emergency/conditional use, special access and WHO emergency use listing

Table 2a: COVID-19 Vaccines by Development Stage

	<i>Count</i>	<i>Percentage of total count</i>
Development discontinued	11	2.50%
Discovery	45	10.10%
Preclinical	236	52.80%
Phase I	40	8.00%
Phase I/II	34	7.60%
Phase II	17	3.80%
Phase II/III	17	3.80%
Phase III	11	2.50%
Regulatory review	3	0.70%
Approved for use	33	7.40%
	447	

Legend: Data from UNICEF, last accessed December 31, 2021 and available at:
<https://www.unicef.org/supply/covid-19-vaccine-market-dashboard>

Table 2b: Summary Statistics of Current COVID-19 Vaccine Pipeline

<i>Total Number of vaccine trials:</i>	<i>530</i>	<i>% of total</i>
Number of vaccine trials by trial phase category:		
Phases, # including		
Early Phase I	4	0.75%
Phase I	129	24.34%
Phase II	54	10.19%
Phase III	92	17.36%
Phase IV	29	5.47%
(blank)	176	33.21%
Not Applicable	68	12.83%
Number of vaccine trials by status category:		
Active, not recruiting	111	20.94%
Completed	24	4.53%
Enrolling by invitation	16	3.02%
No longer available	1	0.19%
Not yet recruiting	97	18.30%
Recruiting	270	50.94%
Suspended	3	0.57%
Terminated	2	0.38%
Withdrawn	6	1.13%

Number of vaccine trials by country category:		
United States (alone)	108	20.38%
United States (involved)	129	24.34%
EU Members (alone)	103	19.43%
EU Members (involved—may overlap if more than one EU member worked on same)	141	26.60%
EU Members (involved—# of vaccine projects)	113	21.32%
China (alone)	41	7.74%
China (involved)	42	7.92%
Russian Federation (alone)	12	2.26%
Russian Federation (involved)	14	2.64%
(blank)	53	10.00%
Other (alone—# of vaccines with only involvement from them)	167	31.51%
Other (involved—# of vaccines including them)	206	38.87%
 <u>Funders (distinct groups/combos)</u>		
Industry	125	23.58%
Industry Other	66	12.45%
Industry U.S. Fed	3	0.57%
Industry NIH U.S. Fed	1	0.19%
Industry U.S. Fed Other	2	0.38%
Industry NIH	3	0.57%
Industry NIH Other	1	0.19%
NIH	8	1.51%
U.S. Fed	1	0.19%
U.S. Fed Other	13	2.45%
Other	307	57.92%

Legend: Data from the US website clinicaltrials.gov, last updated September 30, 2021 and available at: <https://clinicaltrials.gov/>

Table 3: Number of COVID-19 Vaccine Manufacturing Agreements by Vaccine Sponsor and Data Source

Vaccine sponsor	Case study?	Data as of September 1, 2021					Data as of November 19 2021					
		Total agreements UNICEF	Total agreements GHC	Agreement Type GHC			Total agreements UNICEF	Count of doses promised UNICEF	Total number of contracts UNICEF	Total number of doses supplied to date UNICEF	Count of countries to be supplied in agreements to date UNICEF	
				Bulk Substance	Fill and Finish	Full Process						
AstraZeneca/Oxford	yes	25	21	4	4	13	43	4.5b	73	3b	66	
Novavax	yes	12	13	6	1	6	11	2.9b	17	1.6b	15	
Moderna	yes	10	10	2	5	2	32	2.5b	35	1.8b	30	
J&J	yes	9	10		2	8	24	1.7b	19	925m	14	
Pfizer/BioNTech	yes	9	5	1	4	1	98	5.8b	82	4.8b	73	
Curevac	yes	6	7	2	1	3	3	50m	5	n/a	n/a	
Sanofi/GSK	yes						5	1.2b	5	732m	5	

Legend: Data from Global Health Centre (2021). COVID-19 Vaccine Manufacturing Agreements. Graduate Institute of International and Development Studies and UNICEF, last updated November 19, 2021 and available at: <https://www.knowledgeportal.org/covid19-vaccine-manufacturing> and <https://www.unicef.org/supply/covid-19-vaccine-market-dashboard>

Table 4a: Total Doses Agreed to by COVID-19 Vaccine Sponsor

Vaccine sponsor	doses
AstraZeneca/Oxford	4.5bn
Bharat Biotech	750m
CanSino Biologics	26m
Curevac	50m
Gamaleya	500m
ImmunityBio	not reported
Inovio	not reported
Johnson & Johnson	1.4bn
Moderna	2.8bn
Novavax	2.8bn
Pfizer/BioNTech	>6bn
Sinopharm/Beijing	0.8bn
Sinovac	1bn
Vector Institute	not reported

Legend: Data from UNICEF, last updated December 31, 2021 and available at: <https://www.unicef.org/supply/covid-19-vaccine-market-dashboard>

Table 4b: Schedule of COVID-19 Vaccine Doses Delivery

	<i>Product type</i>	<i>half year 1-2021</i>	<i>half year 2-2021</i>	<i>2011</i>	<i>2022</i>	<i>2023</i>
Reported COVID-19 vaccine production Capacity (doses)	all products, stages of development	4.07bn	9.02bn	13.09bn	41.11bn	43.26bn
Reported production capacity (doses)	only products approved for use	2.52bn	5.75bn	8.27bn	26bn	26.27bn
Doses delivered to date	all vaccines			11.7bn		
by type of delivery agreement:	Bilateral/multilateral agreements			5.69bn		
	Donations			0.278bn		
	COVAX			1.089bn		
	AVAT			0.038bn		
	Unknown			5bn		

Legend: Data from UNICEF, last updated December 31, 2021 and available at: <https://www.unicef.org/supply/covid-19-vaccine-market-dashboard>

Table 5a: Drivers of COVID-19 Vaccine Success

Driver 1	Open science related to national and international research and scientific collaborations	shared across candidates
Driver 2	Pre-pandemic knowledge and technology leveraged by innovators	shared across candidates
Driver 3	Regulatory infrastructure and related activities	shared across candidates
Driver 4	IP, licensing and partnering arrangements	varies by candidate
Driver 5	Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries	varies by candidate
Driver 6	Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need	varies by candidate
Driver 7	The willingness of funders to underwrite costs and risks entailed in the development of new vaccines across platforms, companies and countries in advance of approval.	varies by candidate
Driver 8	Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing "at risk" pre-product launch appears to vary by vaccine candidate.	varies by candidate
Driver 9	Vaccine sponsor contracts with other manufacturers to scale up vaccine supply post-approval.	varies by candidate

Legend: Author's classification, details discussed in the text. Vaccine authorized or approval status assessed as of December 31, 2021. Among the sponsors I identified of COVID-19 vaccine candidates, I conducted a web search of public statements regarding product development, intellectual property, licensing and agreements since the inception of the epidemic in January 2020, including in shareholder reports and press releases. I also reviewed public statements the companies made regarding other determinants of product development, success and failure, including financing, manufacturing and meeting regulatory requirements before authorization or approval and following authorization or approval if relevant.

Table 5b: Vaccine Case Study Characteristics

Vaccine case study characteristics		Drivers of success									
		1	2	3	4	5	6	7	8	9	
Vaccine Sponsor for Regulatory Approval or Authorization	Authorized or approved to date in at minimum one OECD country?	Vaccine platform	Open science related to national and international research and scientific collaborations	Pre-pandemic knowledge and technology leveraged by innovators	Regulatory infrastructure and related activities	IP, licensing and partnering arrangements	Willingness of funders to underwrite risks, costs entailed in the development of new technology to meet demand for vaccine/therapeutics across platforms, companies, countries	Advanced purchasing arrangements to guarantee revenue post-approval/post-authorization to manufacturers, assure supply to populations in need	The willingness of funders to underwrite costs and risks entailed in the development of new vaccines across platforms, companies and countries in advance of approval.	Innovators pursuit of manufacturing at scale, including partnerships with other companies, and willingness of funders to support vaccine manufacturing 'at risk' pre-product launch appears to vary by vaccine candidate.	Vaccine sponsor contracts with other manufacturers to scale up vaccine supply post-approval.
Astrazeneca/Oxford	yes	non-mRNA based	yes, shared	yes	yes, shared	yes for manufacturing, clinical trials, regulatory expertise	yes announced candidate vaccine by April 2020	yes, fill and finish and licensing full manufacturing process	yes, extensive; UK government, GAVI, Gates, BARDA/OWS	yes, extensive	yes, extensive
Pfizer/BioNTech	yes	mRNA based	yes, shared	yes	yes, shared	yes for manufacturing, base ingredients, clinical trials, regulatory expertise	yes announced candidate vaccine by April 2020	yes, fill and finish and licensing full manufacturing process	yes, German government, US government support for manufacturing DPA	yes, extensive	yes, fill and finish
NIH/Moderna	yes	mRNA based	yes, shared	yes	yes, shared	yes for base ingredients, manufacturing	yes announced candidate vaccine by April 2020	yes, fill and finish	yes, extensive US government, NIH, BARDA, OWS, CEPI support	yes, extensive	yes, limited
J&J	yes	non-mRNA based	yes, shared	yes	yes, shared	yes lead candidate	yes announced candidate vaccine by April 2020	yes, fill and finish and licensing full manufacturing process	n/a	yes	yes, extensive
Merck/Pasteur/avi	abandoned	non-mRNA based	yes, shared	yes	yes, shared	yes lead candidate	yes, but expressed more hesitation to invest given other core business strategy	n/a	n/a	yes, Merck partnered to support other vaccine manufacturing	n/a
Sanofi/Translate Bio	abandoned	mRNA based	yes, shared	yes	yes, shared	yes lead candidate	yes, but expressed more hesitation to invest given other core business strategy	n/a	n/a	yes, Sanofi partnered to support other vaccine manufacturing	n/a
Curevac	pending	mRNA based	yes, shared	yes	yes, shared	yes for manufacturing, base ingredients, clinical trials, regulatory expertise	yes announced candidate vaccine by April 2020	yes, extensive expected	yes, extensive US government, NIH, BARDA, OWS, CEPI support	yes, diffuse strategy	yes, expected
Novavax	pending	non-mRNA based	yes, shared	yes	yes, shared	yes for manufacturing, base ingredients, clinical trials, regulatory expertise	yes announced candidate vaccine by April 2020	yes, extensive expected	yes, extensive US government, NIH, BARDA, OWS, CEPI support	yes more concentrated strategy	yes, expected

Legend: Summary of case study investigations detailed in the text. Vaccine authorized or approval status assessed as of December 31, 2021. To select case studies, I reviewed the international registry of clinical trials and clinicaltrials.gov to identify COVID-19 vaccine candidates in development since the inception of the epidemic in January 2020. Other data sources that were useful in conducting this review were COVID-19 vaccine trackers, available through various public sources and the peer-review literature, and various preprint services. I selected case study candidates to profile here based on the following criteria: (1) vaccines authorized or approved to date by at least one country’s regulator, (2) a group of vaccine candidates that were abandoned in some phase of development or manufacturing by their sponsors to date, (3) and a group of vaccine candidates that are still in development. I took care to choose among candidates based on different vaccine platforms and those originating in various countries and regions of origin. Among the sponsors of COVID-19 vaccine candidates I identified, I conducted a web search of public statements regarding product development, intellectual property, licensing and agreements since the inception of the epidemic in January 2020, including in shareholder reports and press releases. I also reviewed public statements the companies made regarding other determinants of product development, success and failure, including financing, manufacturing and meeting regulatory requirements before authorization or approval and following authorization or approval if relevant. Last updated December 31, 2021.

Table 6a: Drivers of COVID-19 Vaccine Failure

Driver 1	Pre-approval/authorization scientific risks	varies by candidate
Driver 2	Pre-approval/authorization manufacturing risks	varies by candidate
Driver 3	Post-approval/authorization scientific risks	varies by candidate
Driver 4	Post-approval/authorization manufacturing risks	varies by candidate
Driver 5	Business decisions	varies by candidate

Legend: Author’s classification, details discussed in the text. Among the sponsors I identified of COVID-19 vaccine candidates, I conducted a web search of public statements regarding product development, intellectual property, licensing and agreements since the inception of the epidemic in January 2020, including in shareholder reports and press releases. I also reviewed public statements the companies made regarding other determinants of product development, success and failure, including financing, manufacturing and meeting regulatory requirements before authorization or approval and following authorization or approval if relevant.

Table 6b: COVID-19 Vaccine Case Study Characteristics, Drivers of Failure

Vaccine Sponsor for Regulatory Approval or Authorization	Authorized or approved to date in at minimum one country?	Vaccine platform	Pre-approval/authorization scientific risks	Pre-approval/authorization manufacturing risks	Post-approval/authorization scientific risks	Post-approval/authorization manufacturing risks	Business decisions
Astrazeneca/Oxford	yes	non-mRNA based	moderate	moderate	high	high	n/a
Pfizer/BioNtech	yes	mRNA based	high	high	moderate	high	n/a
NIH/Moderna	yes	mRNA based	high	high	moderate	high	n/a
J&J	yes	non-mRNA based	moderate	moderate	high	high	n/a
Merck/Pasteur/iavi	abandoned	non-mRNA based	high	moderate	n/a	n/a	high
Sanofi/Translate Bio	abandoned	mRNA based	high	high	n/a	n/a	high
Curevac	expected	mRNA based	high	high	n/a	n/a	n/a
Novavax	yes	non-mRNA based	moderate	high	n/a	n/a	n/a

Legend: Author’s classification, details discussed in the text. Vaccine authorized or approval status assessed as of December 31, 2021. To select case studies, I reviewed the international registry of clinical trials and clinicaltrials.gov to identify COVID-19 vaccine candidates in development since the inception of the epidemic in January 2020. Other data sources that were useful in conducting this review were COVID-19 vaccine trackers, available through various public sources and the peer-review literature, and various pre-print services. I selected case study candidates to profile here based on the following criteria: (1) vaccines authorized or approved to date by at least one country’s regulator, (2) a group of vaccine candidates that were abandoned in some phase of development or manufacturing by their sponsors to date, (3) and a group of vaccine candidates that are still in development. I took care to choose among candidates based on different vaccine platforms and those originating in various countries and regions of origin. Among the sponsors I identified of COVID-19 vaccine candidates,

I conducted a web search of public statements regarding product development, intellectual property, licensing and agreements since the inception of the epidemic in January 2020, including in shareholder reports and press releases. I also reviewed public statements the companies made regarding other determinants of product development, success and failure, including financing, manufacturing and meeting regulatory requirements before authorization or approval and following authorization or approval if relevant. Last updated December 31, 2021.

**Comments on the report by Rena Conti:
“The Determinants of COVID-19 Vaccine Success”**

Shanelle Hall*

December 30, 2021

Introduction

When the WIPO Study on the “Determinants of COVID-19 Vaccine Success” began in June, SARS-CoV-2 had taken 3.7 million lives across the world, effective COVID-19 vaccines had been developed with unprecedented speed, and they were being rolled out. Approximately 45 per cent of Americans were fully vaccinated with a 2-dose course, 20 per cent of Europeans, and less than 1 per cent of Africans. While African and other low and lower-middle income countries were behind in receiving COVID-19 vaccines, COVAX shared a plan for vaccines to more equitably distributed by the end of 2021.¹

Since then, the epidemiological situation has changed. By autumn, the Delta variant became the predominant strain in most countries. In early December, only four weeks after being first identified, the more contagious Omicron variant became the dominant strain in South Africa.² The Omicron is projected to be the predominant strain³ in Europe, the United States of America and elsewhere within the coming 1 to 3 months. While COVID-19 vaccines performed well against the original strain and the Delta variant, the Omicron variant is better at evading vaccine-induced immunity. Data is mixed on the severity of disease it causes. Some findings point toward it being milder while others suggest it may lead to more hospitalization in children.⁴ As

¹ “What Does COVAX’s Latest Supply Forecast Tell Us?.” Gavi. Jun. 23, 2021. Web. Apr. 12, 2022. <<https://www.gavi.org/vaccineswork/what-does-covaxs-latest-supply-forecast-tell-us>>.

² “Omicron Is Already Dominant in South Africa.” *The Economist*. Dec. 7, 2021. Web. Apr. 12, 2022. <<https://www.economist.com/graphic-detail/2021/12/07/omicron-is-already-dominant-in-south-africa>>.

³ “Surge in Omicron cases in Denmark and UK sends warning to rest of Europe.” *The Financial Times*. Dec. 13, 2021. Web. Apr. 12, 2022. <<https://www.ft.com/content/3c27c135-fdbc-4db7-8c7c-6e1f6c386235>>.

⁴ European Centre for Disease Prevention and Control (ECDC). “Threat Assessment Brief: Implications of the Emergence and Spread of the SARS-CoV-2 B.1.1. 529 Variant of Concern (Omicron) for the EU/EEA.” Nov. 26, 2021. Web. Apr. 12, 2022. <<https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-emergence-sars-cov-2-variant-b.1.1.529>>.

a result, countries are accelerating their booster dose roll-out. Israel is discussing the timing of a fourth dose.

In terms of vaccine distribution, almost 70 per cent of G7 country populations are fully vaccinated and more than 20 per cent also have received a booster dose. China has fully vaccinated 85 per cent of their population and 9 per cent have received a booster. In contrast, most African countries have vaccinated less than 3 per cent of their populations. Burundi has the lowest reported COVID-19 vaccine coverage in the world of 0.03 per cent. The COVAX goal of all countries receiving vaccines for at least 20 per cent of their populations by the end of 2021 was missed. Poorer countries and countries without vaccine know-how still have very limited access to COVID-19 vaccines.

Since June, the vaccine equity gap has increased, and an additional 1.7 million lives have been lost. The situation further increases the urgency of everyone having access to COVID-19 vaccines—the key tool for saving lives and reducing virus replication.

Summary

In the context of changing epidemiology and increasing vaccine inequity, the WIPO Study of determinants of COVID-19 vaccines success is all the more relevant. The Study provides a timely, important and new analysis on the determinants of vaccine success. The evidence-based analysis that led to the list of determinants is compelling, including the conclusion that patents are a useful incentive but only one of multiple determinants. In my remarks I recommend a look at determinants of overall global vaccine success and failure given the lack of overall vaccine success (access thus far as a future research topic. Including responsibility of patent holders toward the societal goal of saving lives and ending the pandemic; and the suitability of the current global architecture on enabling global access. Lastly, I think the WIPO Study should be shared with countries and regions pursuing pandemic vaccine manufacturing capabilities and capacity because the determinants of COVID-19 vaccine success could be a helpful roadmap for their plans and strategies moving forward.

More than patents—multiple determinants lead to a vaccine’s success

The WIPO Study describes the complexity, costs and risks that are inherent in vaccine development and production. Given the societal value of vaccines, special incentives and action that compensate for these costs and risks are necessary to prevent market failure and incentivize development and production. The case studies and literature review in the WIPO Study show this also to be the case with COVID-19 vaccines.

Patents and intellectual property are used across COVID-19 vaccine development and manufacturing processes. But given the complexity of these processes, the case studies in the WIPO Study show that patents alone are not sufficient. They may not even be an overriding factor. The report uncovers a mix of common factors that have resulted in COVID-19 vaccines being developed, manufactured and distributed in record time with record investment and success: open science in early research, know-how (vaccine regulatory, R&D and technology), collaboration and risk-sharing financial sponsors.

A key conclusion of the study is that no single determinant translates to success but rather multiple determinants. Patents alone are not an enabler.

Individual COVID-19 vaccine success vs. overall vaccine success

After illustrating several successful COVID-19 vaccines, the Study closes with an important note about the current lack of global access to these vaccines. As the Study notes, the COVID-19 vaccine response has been “exceptional in magnitude and speed.” It also has been insufficient. Despite many individual vaccine successes, there is still 55 per cent⁵ of the global population without access. All low-income countries and most middle-income countries are one to two years behind the wealthier countries and/or countries with vaccine know-how.⁶

⁵ World Health Organization (WHO). “WHO Coronavirus (COVID-19) Dashboard: Situation by Region, Country, Territory & Area.” Web. Apr. 12, 2022. <<https://covid19.who.int/table>>.

⁶ Padma, T. V. “COVID Vaccines Will Not Reach Poorest Countries Until 2023.” *Scientific American*. Jul. 6, 2021. Web. Apr. 12, 2022. <<https://www.scientificamerican.com/article/covid-vaccines-will-not-reach-poorest-countries-until-2023/>>.

The definition of vaccine success in the WIPO Study includes distribution of the vaccine to those who would benefit from them. An understanding of an individual vaccine's success and failure is extremely valuable. But analysis of overall success or failure in getting COVID-19 vaccines to those who need them is also needed. The analysis of individual vaccines success does not necessarily provide that insight.

Additional research on the determinants of overall global vaccine success could be helpful. Including a critical look at whether the incentive that patents provide helps or hinders achievement of a societal goal as large as a pandemic response. Or, whether in a pandemic, patent grantees should have a special responsibility⁷ of ensuring access until the societal goal is achieved.

Regional initiatives have emerged in response to a lack of overall vaccine success

Triggered by an initial delay in access to COVID-19 vaccines and growing inequity, several countries and regions created initiatives around local vaccine procurement and production. The African Union (AU) launched the Africa Vaccine Access Trust (AVAT)⁸ in early 2021 with the goal of procuring COVID-19 vaccines directly from the global manufacturing base. AU countries wanted more agency and took the decision to coordinate with, but bypass global mechanisms such as COVAX and UNICEF. The AU recently established an additional goal of manufacturing 60 per cent of the vaccines needed for Africa in Africa by 2040. The Pan American Health Organization (PAHO) recently selected two new mRNA manufacturing

⁷ Oxfam. "Pfizer, BioNTech and Moderna Making \$1,000 Profit Every Second While World's Poorest Countries Remain Largely Unvaccinated." Press Release. Nov. 16, 2021. Web. Apr. 12, 2022. <<https://www.oxfam.org/en/press-releases/pfizer-biontech-and-moderna-making-1000-profit-every-second-while-worlds-poorest>>.

⁸ Africa Union. "African Vaccine Acquisition Trust acquires Covid-19 vaccine doses delivery" <https://africacdc.org/news-item/african-vaccine-acquisition-trust-avat-announces-108000-doses-of-vaccines-arriving-in-mauritius-as-part-of-the-first-monthly-shipment-of-johnson-johnson-vaccines/> AVAT was established by the African COVID-19 Vaccine Acquisition Task Team, set up in November 2020 under the African Union chairmanship of HE President Cyril Ramaphosa, President of the Republic of South Africa, as part of the African Union's COVID-19 Vaccine Development and Access Strategy, and its goal of vaccinating at least 60 percent of the African population with safe and efficacious vaccines against COVID-19. <<https://www.google.com/search?q=Africa+union+avat&oq=Africa+union+avat&aqs=chrome..69i57j0i13.4371j0j9&sourceid=chrome&ie=UTF-8>>.

facilities in Latin America in support of regional vaccine production for the current and future pandemics.⁹ The Inter-American Development Bank is supporting the Forum for the Progress and Development of South America (PROSUR) with a study on increasing vaccine manufacturing in the eight PROSUR member states for future pandemics.

The WIPO Study underscores the importance of these initiatives to strengthen or create regional vaccine production capabilities in areas that have been underserved by the current global architecture. The determinants of COVID-19 vaccine success outlined in the Study provide a roadmap for these initiatives to be a success: establish a base capability on regulatory, research and technology during peacetime (interpandemic), and prepare a strategy to establish a portfolio of vaccine candidates via risk- and cost-sharing agreements with public and private financing sponsors.

In the closing section, the Study points toward the need for “further deployment of special financing” and “collectivizing funding for new vaccine development ... to support the needs of local populations at global scale.” So far, it has not been seen that countries can fairly or equitably prioritize access to one of their sponsored pandemic vaccines with other countries in need.¹⁰ Therefore, if not localized, these recommended actions may perpetuate the risk of lower income countries being subject to the epidemiological context and goodwill of others.

As further action, the WIPO Study could be shared with emerging initiatives on regional and local vaccine production as helpful insight. Moreover, the suitability of the current global architecture could be considered as a part of the research on overall global vaccine success.

⁹ Pan American Health Organization (PAHO). “PAHO Selects Centers in Argentina, Brazil to Develop COVID-19 mRNA Vaccines.” Sept. 21, 2021. Web. Apr. 12, 2022. <<https://www.paho.org/en/news/21-9-2021-paho-selects-centers-argentina-brazil-develop-covid-19-mrna-vaccines>>.

¹⁰ India explicitly nationalized their COVID-19 vaccine manufacturing; and as the report notes, all other vaccines were de facto nationalized via the commercial terms and contracts with their respective governments.

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At the UN, Shanelle spent decades developing and leading \$3.6 billion in world-altering health and humanitarian efforts as UNICEF's Deputy Executive Director and Assistant Secretary General of the UN. She has two decades of experience in engaging with the vaccine industry and governments vaccinating children. She is a Council Member of the World Economic Forum's Fourth Industrial Revolution Artificial Intelligence Council and an Advisor to the Bill and Melinda Gates Foundation. She has been a Board Member and on Board Committees of various organizations including Gavi, the Vaccine Alliance and The Global Fund to fight AIDS, TB and Malaria.

Key roles within the UN include Assistant Secretary General, United Nations/UNICEF (2016–2019); Director of the UNICEF Supply Division (2006–2016); Chief of Immunization, Supply Division, UNICEF / UN (2001–2005). She worked for 10 years in the private sector at Crane Co., an industrial manufacturer. Shanelle holds a Bachelor of Science, Industrial and Systems Engineering, University of Southern California, and Executive Public Administration courses at the Kennedy School of Government, Harvard University.

**Comments on the report by Rena Conti:
“The Determinants of COVID-19 Vaccine Success”**

Axel Metzger*

December 21, 2021

Introduction

The WIPO Study “The Determinants of COVID-19 Vaccine Success” has been completed at a moment where Europe is hit by a fourth and a fifth wave of COVID-19 diseases caused by variants that have first been reported in India (Delta) and South Africa (Omikron). Even though some European countries have reached a high vaccination coverage, the infection rates are still rising. Apparently, a global pandemic can only be controlled if vaccines are available in all affected regions of the world. Therefore, global access to vaccines is key. But the creation and production of vaccines is complicated and costly. The world is depending on innovators who have the necessary technological and financial resources to create vaccines and adapt them to new variants of the COVID-19 pathogen. Their innovation model is based on patents and trade secrets. The last two years have demonstrated that effective vaccines can be created much faster than in the past. However, this fast development was only possible because of unprecedented joint efforts of private companies and public institutions. Much has been achieved with regard to the creation of COVID-19 vaccines whereas a sufficient production and worldwide distribution has not yet been reached. The following comments are not meant as a criticism of the WIPO Study but as suggestions for future research.¹ The comments are written from the perspective of an intellectual property lawyer. Patents and other IP are meant to support technological innovations. Public interest may motivate limitations of the effects of patents or

1 Bowen, William G. “JSTOR and the Economics of Scholarly Communication.” *Journal of Library Administration* 26.1-2 (1999): pp. 27–44. Print. Future research should take into account studies in other languages as English, for example, from German literature Metzger, Axel and Herbert Zech. “COVID-19 als Herausforderung für das Patentrecht und die Innovationsförderung.” *Gewerblicher Rechtsschutz und Urheberrecht* 122.6 (2020): pp. 561–569; Bäumler, Jelena and Jörg Philipp Terhechte. “Handelsbeschränkungen und Patentschutz für Impfstoffe.” *Neue Juristische Wochenschrift* 73.48 (2020): pp. 3481–3487; Böni, Franz and Alex Wassmer. “Kartell- und wirtschaftsrechtliche Beurteilung der Aussetzung von Patenten.” *Europäisches Wirtschafts- und Steuerrecht* 4 (2021): pp. 205–207; Haase, Martin S. “Einschränkungen des Patentschutzes für Arzneimittel – Auf der Suche nach geeigneten rechtlichen Kriterien zur grundrechtskonformen Abwägung der kollidierenden Interessen.” *Innovations- und Technikrecht* 3 (2021): pp. 154–158; Hauck, Ronny. “Gibt es die Know-how-Zwangslizenz?” *Gewerblicher Rechtsschutz und Urheberrecht in der Praxis* 13.12 (2021): pp. 333–335; Lunze, Anja and Jan Phillip Rektorschek. “Auswirkungen von COVID-19.” *Pharmarecht* 43.11 (2021): pp. 629–636; Richter, Carsten. “Die staatliche Benutzungsanordnung in Zeiten der Corona-Pandemie.” *Mitteilungen der deutschen Patentanwälte* 112.1 (2021): pp. 1–4; Stierle, Martin. “Ausschließlichkeit in der (Corona-)Krise – Über Alternativen und Zugangslösungen im pandemielevanten Innovationsermöglichungsrecht.” *JuristenZeitung* 76.2 (2021): pp. 71–80.

justify compulsory licenses. But these limitations of patent law must be complemented by other more appropriate policies and initiatives to achieve worldwide supply and equitable access to vaccines.²

Necessary limitations of the research question

The focus of the WIPO Study is to determine the role of different aspects of open science, of push and pull mechanisms, of patents, of trade secrets/know-how, of licenses and of public agencies both for the creation of COVID-19 vaccines and for their production and distribution. This holistic approach is both necessary and ambitious. However, put as a general question, at least at this point in time, it seems hardly possible to produce straight-forward answers since the role of these determinants seems to be different for the various vaccine candidates examined. It is therefore for good reasons that the Study takes a more modest approach, which is to describe the determinants in the general parts of the paper and then look into case studies and explain their specific role in the different scenarios. It would require a large-scale study to confirm or reject comparative hypothetical statements such as faster/slower with/without IP, more/less public/private funding, open science, etc. Such a large-scale study would have to cope with the difficulty that the starting points of the examined vaccine candidates were considerably different. This could be interesting for more detailed future research but would have clearly exceeded the resources available for the WIPO Study.

Observed market failures in the development of vaccines

The WIPO Study describes the specific market failures in the development of vaccines that have been observed in the last decades. These market failures concern in particular vaccine platforms, the basic technologies used for different kinds of vaccines and diseases that are mostly found in the Global South. It is remarkable how the joint private and public efforts have overcome these market failures in the case of COVID-19 vaccines. The WIPO Study shows the determinants of this unprecedented success of vaccine development. One can hope that some of the technological advances made regarding vaccine platforms will support a faster development from viral sequencing to clinical trials for other pathogens as well.³ Still, it is difficult to imagine that the industrialized states of the North will engage in comparable risk-mitigation and other push and pull incentives with regard to diseases essentially found in the southern hemisphere. Therefore, the positive lessons learned from the development of COVID-19 vaccines will not be easy to transfer to other pathogens.

The positive functions of patents in vaccine development

The WIPO Study describes how patents support innovation by allowing patent holders to exclude others for a limited term. The right to exclude others in turn allows innovators to charge prices that are

2 Major initiatives are COVAX, GAVI and CEPI.

3 Lurie, Nicole, Melanie Saville, Richard Hatchett and Jane Halton. "Developing Covid-19 Vaccines at Pandemic Speed." *New England Journal of Medicine* 382.21 (2020): pp. 1969, 1970.

above marginal costs of production. The hope for exclusivity can incentivize innovators to invest in research and development. Future research could explore additional functions of patents for vaccine development: (1) Patents play a decisive role for all kinds of technology transfers. They serve as the basis for licenses. Much technology would not be shared if innovators could not define the terms of use and reserve their rights. As clearly defined property rights, patents help to lower transaction costs.⁴ Patents may support technology transfer to the Global South. Cooperation with vaccine producers may be facilitated if the respective markets provide adequate patent protection.⁵ (2) Patents serve as signaling tools for start-ups and SMEs seeking financial resources. Patent portfolios play an important role to convince venture capital investors or partners from major pharmaceutical industries.⁶

Relationship of patents and trade secrets

A closely related issue that deserves more attention in future research is the relationship of patents and trade secrets in vaccine development. Patents allow and oblige innovators to disclose their technologies. Without legally guaranteed exclusivity, they would keep their inventions as trade secrets. Under a patent system, the innovator discloses its invention in the patent registry in return for exclusivity for a limited term. However, it has become clear during the public debate on a possible TRIPS waiver⁷ that the information disclosed in the patent claims and patent descriptions as such does not enable competitors to start vaccine production. For the time being, it seems to be difficult to reproduce vaccines without the secret know-how of the inventor. This seems to be particularly the case for mRNA vaccines. The special know-how of manufacturers is partly kept secret because it does not relate to patentable information, but in some cases, it is deliberately not published as part of the patent application.⁸ In contrast to other pharmaceuticals, it is not possible to successfully reverse engineer a vaccine, as an identical product is not guaranteed if an alternative production process is used.⁹ Therefore, access to secret manufacturing information is key for vaccine production. This overlap of patents and trade secrets distorts the “grand bargain” between inventor and society. The innovator can claim exclusivity but the disclosure of its technology does not enable competitors. This know-how aspect complicates any regulatory adjustments of the patent system. Compulsory licenses or statutory

4 So-called “prospect theory,” see Kitch, Edmund W. “The Nature and Function of the Patent System.” *Journal of Law and Economics* 20.2 (1977): pp. 265, 278.

5 Crager, Sara Eve. “Improving Global Access to New Vaccines: Intellectual Property, Technology Transfer, and Regulatory Pathways.” *American Journal of Public Health* 104.11 (2014): pp. e85–e91.

6 Haeussler, Carolin, Dietmar Harhoff and Elisabeth Mueller. “How Patenting Informs VC Investors – The Case of Biotechnology.” *Research Policy* 43.8 (2014): pp. 1286, 1293, 1295 f.; Hottenrott *et al.*, *Economics of Innovation and New Technology* 25 (2016): pp. 197, 201, 212 f.

7 See WTO documents IP/C/W/669 and IP/C/W/669/Rev.1 on the proposal for a “Waiver from certain provisions of the TRIPS agreement for the prevention, containment and treatment of COVID-19.”

8 Price, W. Nicholson, 2nd, Arti K. Rai and Timo Minssen. “Knowledge Transfer for Large-Scale Vaccine Manufacturing.” *Science* 369.6506 (2020): pp. 912, 913.

9 Crager, *op. cit.*; Price, W. Nicholson, 2nd and Arti K. Rai. “Drug Development: Are Trade Secrets Delaying Biosimilars?.” *Science* 348.6231 (2015): pp. 188 f.

waivers will not allow third parties to produce mRNA vaccines if limited to patents. The problem of access to know-how and manufacturing information for vaccines has long been known,¹⁰ but now receives greater public attention.

The role of patent-protected basic technologies

Political claims for a statutory waiver or for voluntary patent pledges of vaccine innovators are oftentimes based on simplifications and misconceptions of the current landscape of patents related to COVID-19 vaccines. COVID-19 vaccines could only have been developed since early 2020 after the emergence of the pathogen. The earliest patent applications for COVID-19 vaccines are currently published after the 18-months period. These patent applications are still far off having endured the examination and possible post-grant opposition procedures. Therefore, at this point in time, the relevant patents to be taken into account are patents on basic technologies that are used for the production of or as compounds of COVID-19 vaccines. These patents on basic technologies may trigger legal conflicts and as a consequence slow down research and development by follow-on inventors. The Moderna/Arbutus conflict illustrates the legal uncertainties arising out of conflicts over patents on basic technologies.¹¹ The WIPO Study addresses this conflict with regard to lipid nanoparticle technology. A second basic technology mentioned in the WIPO Study that is needed by nearly all developers of COVID-19 vaccines is a technology invented by the NIH to “freeze” the coronavirus spike proteins to the prefusion state.¹² One could add as a third basic technology a vaccine technology invented at the University of Pennsylvania in 2005. The invention allows mRNA to be administered to the body without eliciting an immune response. This technology is used by all mRNA vaccines.¹³ For the time being, notwithstanding the conflict over the validity of the Arbutus patent, it seems that vaccine innovators could get licenses for the necessary basic technologies. However, it is not unlikely that the rapid development of vaccine and more general mRNA technology may soon create patent thickets which may then call for patent pools. Also, basic technologies may develop into industry standards that may require FRAND licensing schemes.

Intellectual property resulting from public funded research

The WIPO Study aims at determining the role of different determinants for the creation of COVID-19 vaccines, in particular open science, push and pull mechanisms, patents and the role of public agencies.

10 Crager, *op. cit.*; Price, W. Nicholson, 2nd and Arti K. Rai. “Drug Development: Are Trade Secrets Delaying Biosimilars?.” *Science* 348.6231 (2015): pp. 188 f.

11 *Moderna, Inc. v. Arbutus Biopharma Corp.*, US CAFC, December 1, 2021, Case 20-1184. See also Gaviria, Mario and Burcu Kilic. “A Network Analysis of COVID-19 mRNA Vaccine Patents.” *Nature Biotech* 39.5 (2021): pp. 546, 547 and fig. 1.

12 Rizvi, Zain. “Leading COVID-19 Candidates Depend on NIH Technology.” Public Citizen. Nov. 10, 2020. Web. Apr. 12, 2022. <<https://www.citizen.org/article/leading-covid-19-vaccines-depend-on-nih-technology/>>; Gaviria and Kilic, *op. cit.*, pp. 546, 548.

13 Gaviria and Kilic, *op. cit.*, pp. 546, 547 and fig. 1.

This complex picture should be complemented by a closer look on the consequences of public funding for the resulting patents and trade secrets. In the United States of America, universities hold broad patent portfolios. Some of the relevant basic technologies necessary for the production of mRNA vaccines are held by universities, as mentioned before. However, in the United States of America publicly funded inventions may be covered by the Bayh-Dole Act, which allows small businesses, universities and non-profit organizations to own inventions funded by taxpayers' money but provides march-in rights for the government.¹⁴ In the context of COVID-19 vaccines, at least several basic technologies developed by the University of Pennsylvania and covered by the Bayh-Dole Act are used for mRNA vaccines.¹⁵ As a result Pfizer/BioNTech and Moderna acquired non-exclusive licenses for this technology.¹⁶ In Europe, some jurisdictions and public funding institutions allow the recipient private companies to register the resulting patents, whereas other jurisdictions and funding agencies follow different strategies.¹⁷ With regard to funding on a European level, the lack of legal requirements for a rapid and wide access to the funded innovations has been criticized. The European Union collected 9.9 billion euros during the Global Response Pledging Conference (GRPC) for the development of COVID-19 vaccines and treatments. However, there has not been a public announcement that the funded technologies have to be shared for fair prices or licensed under non-exclusive licenses.¹⁸ Other financial projects to promote innovation in the European Union, such as HORIZON 2020 or HORIZON Europe, are even explicitly allowing participants to transfer rights under exclusive licenses.¹⁹ Given the very relevant contribution of taxpayer's money to the creation of COVID-19 vaccines and the controversial discussion in Europe, future research should shed additional light on the role of publicly funded inventions.

Assessing the different functions of licenses

Licenses for use of IP protected technologies play an essential role for the creation and distribution of vaccines. Licenses prevent blocking effects of patents on basic technologies that are used by vaccine innovators. They provide a basis for the production and distribution of vaccines and compounds by manufacturers and distributors. Vaccine innovators do only engage in such cooperation on the basis of clear stipulations about the use of their patents and trade secrets. Otherwise, they would endanger their

14 35 U.S. Code § 203.

15 Abinadar, Luis Gil, "Foundational mRNA Patents Are Subject to the Bayh-Dole Act Provisions." KEI. Nov. 30, 2020. Web. Apr. 12, 2022. <<https://www.keionline.org/34733>>.

16 Gaviria and Kilic, *op. cit.*: pp. 546, 547; Abinadar, *op. cit.*

17 Bagley, Constance E. and Christina D. Tvarnø. "Promoting 'Academic Entrepreneurship' in Europe and the United States: Creating an Intellectual Property Regime to Facilitate the Efficient Transfer of Knowledge from the Lab to the Patient." 26 *Duke Journal of Comparative & International Law* 1.1 (2016). <https://scholarship.law.duke.edu/djcil/vol26/iss1/1>.

18 van Overwalle, Geertrui. "Will Covid Patents Save the World?" *Gewerblicher Rechtsschutz und Urheberrecht International* 69.9 (2020): pp. 883–884.

19 Article 44 of Reg. 1290/2013 and Article 40 (3) of Reg. 2021/685. Exceptions are Article 44 (3) of Reg. 1290/2013 and Article 40 (4) of Reg. 2021/685 which grant the Commission a veto right against transfers to non-EU-party transfers.

business model. Licenses ensure technology transfer on a national and international level. And finally, licenses may be used as a proxy to determine the relevance of a technology protected by patents and trade secrets.²⁰ However, licenses are for most part not publicly available. Empirical studies on licenses are restricted to reviews of public statements of companies,²¹ a method also applied by the WIPO Study in the framework of the case studies. The specific provisions of the license contracts and the amounts of license fees remain confidential in most cases. This makes it impossible to come to definitive conclusions about the role of licenses for vaccine creation and production. It would be highly desirable for future research to have a broader empirical basis with regard to the relevant license agreements.

Case studies from other world regions

The WIPO Study examines both successful and so far unsuccessful COVID-19 vaccine candidates in several case studies. This provides additional insights and exemplifies how diverse the starting points and conditions of the different vaccine development projects were. The chosen candidates for case studies are all from developed industries in North America and Europe. It would be of interest to learn more about the development of vaccines in other regions of the world, in particular in China and Russia.

Emerging landscape of COVID-19 vaccine patents

Due to the 18-month publication period, the first patent applications for COVID-19 vaccines from early 2020 are currently becoming publicly available. It is not certain when these patents will finally be granted and how the final wording of the claims will look after examination and possible opposition procedures. Moreover, it remains to be seen how the patents in their final wording will correlate and which of the claimed priorities will be the earliest. One can expect that the number of patents claiming or being related to COVID-19 vaccines will rise in the coming months. At this point in time, only a few patent applications of the major vaccine producers covering COVID-19 have been published,²² whereas a search on Patentscope shows many Chinese and Russian applications.²³ It may well be that the discussion of the role of patents could be different once the number of published patent applications rises.

20 Gaviria and Kilic, *op. cit.*, 546, 547.

21 Gaviria and Kilic (*op. cit.*) refer to US Securities and Exchange Commission (SEC) filings of reported license agreements.

22 See EP 3901260 A1 (Biontech), WO 2021/197589 A1 (Biontech), WO 2021/156267 A1 (Curevac), WO/2021/159130 (Moderna), WO2021231963 (Moderna).

23 A search using the terms “SARS” and “Vaccine” on the “Front Page” resulted in 93 patent applications for technologies related to vaccines with reference to China and 10 patent applications with reference to Russia. Using the terms “COVID” and “Vaccine” resulted in 60 patent applications with reference to China and seven with reference to Russia.

Blocking effects of COVID-19 vaccine patents

The WIPO Study refers to the tradeoff of patents as aiming to balance incentives for innovation, so called dynamic efficiency, with incentives for affordability and access, so-called static efficiency. The current public debate on a possible waiver of patents for successful COVID-19 vaccines is claiming that the crisis calls for a greater emphasis of the access paradigm. Future research should further investigate whether COVID-19 patents entail blocking effects, especially with regard to access to vaccines in the southern hemisphere. For the time being, there seems to be no evidence of any such blocking effects. Patent holders seem to cooperate so far, if pharmaceutical companies from the Global South are technically equipped to enter into vaccine production. Moreover, there are no reported cases or legal conflicts with regard to compulsory licenses for COVID-19 vaccine patents. This situation may change in the future. It may turn out that the existing legal instruments for access to technologies do no longer suffice. But in the current situation, regulators are better advised to take a cautious approach as long as the global community is in urgent need for innovative technical solutions to overcome the crisis.

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