THE TIMELINES AND IMPLICATIONS FOR COVID-19 VACCINES

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This is the second of two articles on the outlook for and potential timing of treatments and vaccines for COVID-19. The goal is to provide practical assessments of the health care industry's efforts for business leaders and public health officials who need to plan for the future of their companies and communities. In this article we examine the outlook for a vaccine or vaccines. It is based on broader research conducted by the BCG scientist network, which comprises more than 500 individuals around the world with advanced degrees (MDs and PhDs) and relevant private-sector experience.

When will an effective vaccine be available for COVID-19? This is the question everyone is asking and that will very likely determine when society can confidently return to a pre-COVID world.

Any assessment of the potential availability and timing of a vaccine requires an understanding of four factors:

- **Epidemiological Uncertainty.** Market potential has traditionally been a commercial barrier in the development of global health vaccines. Perhaps ironically, uncertainty about the availability of a COVID-19 vaccine is heightened because, as the incidence of disease declines (because of social distancing and other measures), rapid testing becomes more challenging. The availability of high-quality serological antibody tests in the hands of trained epidemiologists should help, as will funding commitments that de-risk and accelerate development.
- **Scientific Uncertainty.** Developing a successful vaccine is complex, particularly against a new pathogen about which the scientific knowledge is still nascent. The success rate of vaccine candidates is typically 10% or less from preclinical studies through clinical trials to licensure.[1]
- **Proof of Safety and Efficacy.** It usually takes five to ten years to generate a clinical package that can gain regulatory approval for use.

- **Manufacturing at Scale.** Once a vaccine is scientifically validated, it must be produced at a scale that can enable herd immunity (which can result from either vaccination or previous infection) on a global scale. That will probably mean coverage of more than 60% of the world's population, which could require up to 5 billion doses for a single-dose vaccine and more than 10 billion doses for a multidose vaccine.[2] The sheer scale of production highlights the importance acting decisively now to address manufacturing needs. We must also ensure that infrastructure can be adjusted or reallocated depending on which vaccine ultimately shows the most promise.

Both the public and private sectors are dedicating significant resources to finding innovative ways to address these issues. Multiple activities typically performed in sequence are now being done in parallel, at significant financial risk. The need to generate clinical data to demonstrate safety and efficacy, combined with the need to reach global manufacturing scale, mean that producing a vaccine in the necessary amounts will probably not be possible for at least 12 to 18 months—and this is a best-case timeline—or the second to fourth quarters of 2021. An early release in limited volumes for emergency use in high-risk groups could take place later this year, assuming positive data and approval from regulators. This would likely be in the range of millions of doses.

The 12- to 18-month timeline assumes that a vaccine progresses through all of the various stages of testing without encountering significant issues. A longer timeline of 24 to 36 months (2022 to 2023) would still represent a record in vaccine development. Given the complexity of vaccine programs, it is prudent to plan for scenarios in which rollout takes longer. (See our first article, on the outlook for COVID-19 therapeutic treatments.)

Below we examine the current pipeline of candidate vaccines, the factors involved in achieving scientific confidence in a vaccine, and the investments that need to be made now to enable manufacturing at sufficient scale.

Some Factors Affecting Vaccine Development

COVID-19's similarities to SARS and MERS have allowed researchers to accelerate development, building on prior research related to those coronaviruses. As of mid-April 2020, more than 115 vaccine candidates were in development. This kind of broad pipeline is critical, given that infectious disease vaccines typically achieve end-to-end success rates of less than 10% and may have different safety and efficacy profiles in different subpopulations.

There will be inevitable tradeoffs associated with different classes of vaccine. For example, variations in immune response in elderly populations may necessitate a higher dose or the inclusion of an immune-boosting adjuvant, the need for which could vary by vaccine. Storage requirements will create supply chain issues, particularly in developing markets, highlighting the difficulty of developing a vaccine that works safely and effectively across populations and geographies.

Right now, we do not know whether COVID-19 will persist, re-emerge in a second wave, or become a seasonal threat (like influenza) or an endemic pathogen. Epidemiology will have a big impact on the ability to accelerate development. The group at the Jenner Institute at Oxford University that is behind one well-publicized candidate vaccine has expressed concerns about its ability to execute Phase II and III trials quickly in the UK if the number of cases continues to decline in the coming months. Despite this uncertainty, action is required now to make the significant investments needed to realize an aggressive timeline.

Achieving the 12- to 18-Month Timeline

Multiple vaccine modalities are in development and in clinical trials, including tradi-

tional protein subunit vaccines, whole-cell vaccines, and more novel nucleic acid-based technologies. As clinical data becomes available, we will have a better understanding of which approach is most likely to succeed against COVID-19. We have limited data so far on the rate of mutation in this virus, which will affect how effectively a potential vaccine will work (although mRNA technologies, among others, may be suited to rapidly adjusting the vaccine or to combining multiple antigens, if necessary).

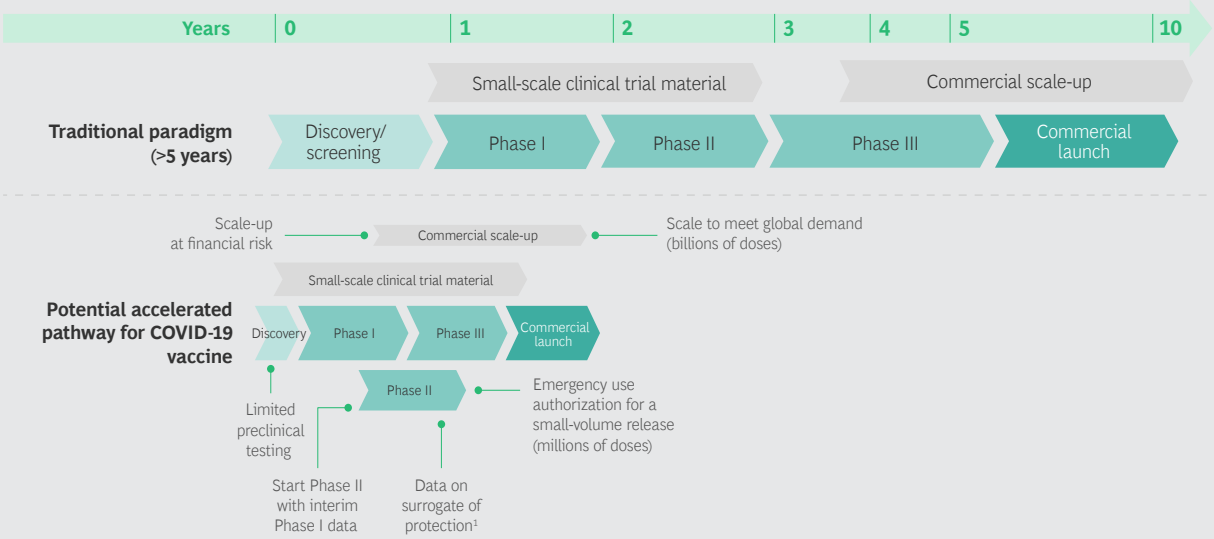
Traditional vaccine development involves planning, recruiting patients for, and executing each of three clinical trial phases and generating the data necessary to design each one. A vaccine must be shown to be safe (Phase I), which typically involves 6 to 12 months of data collection after each patient is dosed. Phase II trials provide an understanding of the dosages required, and Phase III is a full efficacy study. As companies gain greater confidence that a vaccine will work, they begin to prepare for commercial launch. The entire process generally takes five to ten years.

A 12- to 18-month timeline would be unprecedented, but we live in unprecedented times. (See Exhibit 1.) To execute it, companies will need to:

- Develop the dedicated resources and support needed at clinical sites to rapidly recruit, dose, and capture data from patients
- Engage with regulators on study designs and on the possibility of moving to subsequent study phases despite limited data (as occurred with CanSino Bio's vaccine, discussed below).
- Invest in scale, at significant financial risk, to build internal manufacturing capacity, and form partnerships to expand short-term manufacturing capacity.

The Fast Movers. At the time of writing, seven vaccine candidates from six pharmaceutical companies and academic institutions—Moderna, Inovio, CanSino Bio, Oxford University's Jenner Institute, Sinovac, and Shenzhen Genoimmune Medical Institute—had already made it into clinical trials. None of these organizations has previously taken a vaccine through to commercialization, so partnerships will be key.

EXHIBIT 1 | Companies Are Moving Aggressively to Accelerate COVID-19 Vaccine Development



Source: BCG analysis.
[1]There are currently no clear markers associated with long-term protection against COVID-19; to support a surrogate of protection endpoint, these markers would have to be defined.

The vaccine from China's CanSino Bio is the most advanced; the company is currently using QR codes to virtually enroll patients in a Phase II trial. The US company Moderna, in partnership with the Coalition for Epidemic Preparedness Innovations (founded by the Bill & Melinda Gates Foundation and the Wellcome Trust) and the National Institute of Allergy and Infectious Diseases (part of the National Institutes of Health), produced the first clinical batch of its candidate vaccine, which uses new nucleic acid-based mRNA technologies, for Phase I studies 42 days after sequence selection—a record pace. Given the importance of a vaccine for the elderly, the NIH has since expanded the patient population in these trials to include adults over age 56 (including a cohort aged 71 and older).

Other vaccine candidates using mRNA technologies, being pursued by companies such as BioNtech, as well as the DNA-based technology of Inovio, are on similar promising trajectories, but these approaches do not have the same level of historical safety and efficacy data with which to work as more traditional technologies.

The Traditional Big Players. Large pharma companies will likely seek to leverage their global infrastructure to move quickly once their vaccines enter clinical trials, hoping for faster end-to-end results on the basis of their previous experience with vaccine development. Pfizer has partnered with BioNTech, a leading mRNA player, and as of late April 2020 they were close to beginning trials. Johnson & Johnson aims to quickly advance its platform technology for vaccine production by utilizing its experience and infrastructure to expedite clinical trials. The company has publicly stated that it is scaling up production capacity to about 1 billion doses. Sanofi and GlaxoSmithKline have formed a unique partnership to develop a vaccine with an immune-boosting adjuvant using technology from both companies; they, too, aspire to have 1 billion doses of their vaccine candidates ready within 12 to 18 months.

Accelerating Rollout. As multiple additional players prepare for clinical development, a couple of potential levers could accelerate rollout, but they come with tradeoffs and risks:

- **Using Interim Data Readouts.** Typically, companies wait for full clinical data before progressing to the next phase of testing. In the race for a COVID-19 vaccine, however, companies are preparing for trials based on interim data. CanSino Bio has used interim safety data from one month of Phase I trials to support Phase II trials in China. This comes with a level of risk that regulators will likely assess carefully. In the US, Moderna recently submitted an application to conduct Phase II trials of an investigational new drug in the second quarter of 2020; 300 18- to 55-year-old volunteers and 300 volunteers over age 55 would receive two doses and be evaluated over the course of a year. In a public statement, Moderna has suggested that it could potentially start conducting Phase III trials by the fall of 2020, even as the earlier trials are still in progress.

- **Accelerating Efficacy Readouts.** In areas where the virus is endemic, it may be possible to quickly obtain an assessment of efficacy. But if the number of cases continues to fall, efficacy testing could be more challenging and require alternative approaches. One possibility is demonstrating early efficacy using a "challenge study" for vaccines that have proven safe in an infection model. However, there are no current models in place, nor is there a clear understanding of what immune markers are associated with a protective response.

  Some researchers have proposed a human infection study in which volunteers would be exposed to the virus in a controlled environment post-vaccination. This approach raises many ethical questions and would likely require the availability of effective therapeutics to mitigate potential harm to volunteers. These types of studies were conducted in the past for influenza, malaria, and noroviral illnesses and typically require

healthy volunteers at low risk for severe illness.

Other Variables. Some people generate an insufficient immune response to vaccination and therefore require a second dose. There is also a pressing need for a vaccine for people over 60, and age-related changes in the immune system may affect responses in that segment of the population. For these reasons, it will be important to ensure that clinical trials have sufficient coverage of patients over 60 years old.

Given how much is unknown about COVID-19, a multidose vaccine is likely, and this further exacerbates the manufacturing challenge. Moderna and Johnson & Johnson have received significant investment commitments from the Biomedical Advanced Research and Development Authority (part of the US Department of Health and Human Services) to support scale-up efforts.

In late April, a number of companies formed partnerships with the goal of scaling up production. Johnson & Johnson is partnering with Catalent and Emergent BioSolutions and is also investing internally to build additional capacity. Moderna's partnership with Lonza aims to produce up to 1 billion doses (assuming the low dose of clinical trials). (See Exhibit 2.) AstraZeneca has partnered with Oxford's Jenner Institute for global manufacturing and distribution rights. In China, Sinovac has announced plans to build a 223,000-square-foot plant that could supply about 100 million doses a year. These are positive steps, but manufacturing the antigen is only one piece of the scale challenge, which should not be underestimated. A big bottleneck will be in the final fill-finish processing of the vaccine (see below).

Extraordinary Times Call for Innovative Ways of Working

Given the exceptional public health and economic burden that COVID-19 is inflicting on society, regulators in different parts of the world (such as the US Food and Drug Administration and the European Medicines Agency) will likely work with companies in partnership in order to accelerate (or develop alternative) approval pathways. This will be particularly important for companies that have not yet developed a commercial vaccine. In essence, reg-

EXHIBIT 2 | Two Vaccines Highlight the Difficulties and Costs of Achieving the Required Scale

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Technical overview	• mRNA-based technology formulated inside a lipid nanoparticle	• Viral vector with COVID-19 S-antigen conjugated to surface
Most advanced clinical program	• Phase II (cytomegalovirus vaccine)	• Phase III (HIV vaccine)
Current stage of COVID-19 vaccine	• Midway through Phase I testing • Investigational new drug (IND) application filed to start Phase II in summer, 2020	• Preclinical/Phase I likely by summer, 2020; plan to use global network to accelerate trials
Current scale	• 75–150 gram batch (600,000–1.5 million doses/month based on reported clinical doses)	• 1,000 liter scale reported (~25 million doses/month or 300 million doses/year)
Likely scale by yearend	• Scaling not dependent on cell culture, which may enable easier scale-up; up to 10x increased capacity expected by yearend • Partnered with Lonza to expand capacity	• Establishing master seed cell line and building new plant to produce 50 million doses/month in 2021 • Partnered with Catalent and Emergent to expand capacity
Timeframe to reach global scale	• >12 months to reach scale, depending on partnerships with major player or significant capital investment	• 1 billion doses over the next ~12 months considered realistic
Probable level of investment required	• Up to ~$483 million committed by BARDA[1] • Additional investments likely required for fill-finish support	• ~$1 billion investment likely required (split between J&J and BARDA[1])

Sources: Company press releases, BCG analysis.
[1]Biomedical Advanced Research and Development Authority.

ulators will play a more active role in shepherding development efforts, moving drugs more efficiently through the various phases by:

- Providing counsel on a geographic strategy for site selection
- Advising on clinical trial protocols
- Advising on trial design and execution
- Reviewing data at intervals instead of waiting for final data readouts

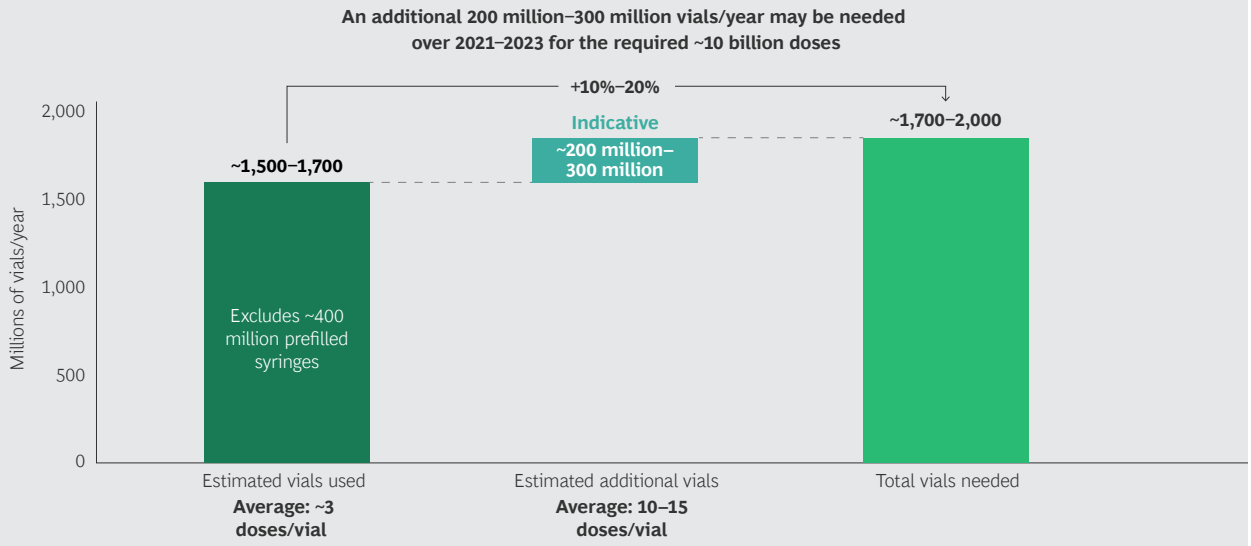
In the US, the FDA's Emergency Use Authorization will probably be the fastest route to a controlled, small-scale release. It would require a clear safety profile for initial dosing and an early indication that a vaccine generates an effective immune response. Multiple vaccine players have indicated that once they have generated appropriate safety data in clinical trials (which takes about six months), they will apply for this authorization for perhaps a million doses or less. That would mean a potential small-scale release in the third quarter of 2020, which is Moderna's goal and also the timeline announced by the Jenner Institute following successful animal trials.

Other avenues that have been considered in the past to accelerate vaccine approvals are the Animal Rule (used in Ebola) and the use of "surrogates of protection." In the case of a vaccine for COVID-19, however, these are currently not viable options because there is neither an established animal model nor a clear understanding of the markers associated with long-term protection.

A Race to the Fill-Finish Line

A critical step required in the production of all vaccines is sterile fill-finish. This is the process of filling the liquid vaccine into a sterile vial, which is a highly regulated task with limited capacity. Given the expected scale of demand, a multidose vial will likely be required (that is, one vial will contain enough vaccine to dose multiple people). Currently, there are about 6 billion vaccine doses produced annually, involving 1.6 billion vials. Estimates of the demand for a COVID-19 vaccine suggest that about 200 million to 300 million additional multidose vials will be required (assuming multiple doses in each vial). (See Exhibit 3.) This will place enormous strain on the supply of vials and on the infrastructure needed to produce them.

EXHIBIT 3 | A COVID-19 Vaccine Will Require an Estimated 10% to 20% Increase in Vial Filling Capacity and a Shift To Larger Formats



Sources: Industry interviews; BCG analysis.

While some capacity is available as part of pandemic flu preparations, six global actions may still be required to ensure that fill-finish capacity is available for a COVID-19 vaccine:

1. Collaborate across the industry to manage capacity within pharma companies and contract manufacturing organizations and to enable appropriate reallocation for the most promising candidates as the landscape evolves.

2. Pull forward production and stockpile existing vaccines (or therapeutics) by, for example, producing flu vaccine earlier to avoid competition for the same capacity.

3. Standardize vaccine fill so that manufacturers can prepare lines, build inventory, and easily reallocate capacity to leading candidates.

4. Reconfigure existing production lines to enable more multidose vial filling and to optimize production flows (such as lab shifts) to increase output.

5. Engage early with suppliers on stoppers, vials, and other materials, particularly for larger-vial formats.

6. If the preceding measures prove insufficient, build additional capacity rapidly to ensure rapid scale-up and commercial rollout.

The Importance of Partnerships

Given widespread actions to "flatten the curve," it is likely that we will see a decline in cases well before treatments or vaccines come to market. There is a risk that this could undermine momentum, as occurred with GlaxoSmithKline's Ebola vaccine, which encountered difficulties progressing through Phase III trials as the number of cases dwindled toward the end of the 2014–2016 epidemic. This prospect creates significant uncertainty for those developing vaccines and reinforces the need for sustained investment through both external funding and partnerships.

Funding from governments, NGOs, philanthropies, and cross-industry partnerships will all likely play a key role.

A number of such initiatives are already in the works. As of mid-April, the US government had committed up to $3.8 billion in funding, with the Biomedical Advanced Research and Development Authority already committed to provide up to $1 billion to Johnson & Johnson and Moderna to support their respective vaccine programs. In the UK, the government has pledged the equivalent of about $680 million, of which $320 million has already been committed to the Coalition for Epidemic Preparedness Innovations. Germany has committed $150 million to CEPI. The World Health Organization has committed up to $8.7 billion, split between vaccines and therapeutics, through the Access to COVID-19 Tools (ACT) Accelerator.

The Bill & Melinda Gates Foundation has committed more than $250 million thus far and has begun to discuss investing in manufacturing capacity. Partnerships with WHO, CEPI, and governments will be critical to manage distribution, stockpiling, and coordination of vaccine administration. Cross-industry partnerships may be required to share capacity, particularly in the short term, to address high-priority bottlenecks such as fill-finish.

CRISES CRAVE RESOLUTION, of course, and they also give birth to misleading as well as robust information. Decision makers in health care and business need sound data and projections based on clear-eyed assessments of the possible. Treatments for COVID-19 will come to market, and there is high hope that a successful vaccine will be found. But the difficulty should not be underestimated. If we can find a successful vaccine, going from successful trials to widespread inoculation will be a huge challenge. There's value in pushing aggressively toward solutions, but it also pays to keep efforts rooted in reality. Our toolsets will grow over the next six months. In the best-case scenario, the end will be in sight within a year. But we must

be ready for a long fight and continue to buy time to do the work needed to determine which instruments of human ingenuity will be the ones to finally deliver us from COVID-19.

NOTES

1. Pronker, E., et al, "Risk in Vaccine Research and Development Quantified," *PLOS ONE*, Volume 8, Issue 3, March 2013.

2. Altman, D., et al., "What Policy Makers Need to Know About COVID-19 Protective Immunity," *The Lancet*, April 27, 2020.

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