THE SABIN-ASPEN
VACCINE SCIENCE
& POLICY GROUP

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Powering Vaccine R&D:

OPPORTUNITIES FOR TRANSFORMATION

Foreword by Harvey V. Fineberg and Shirley M. Tilghman

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ABOUT THE SABIN-ASPEN VACCINE SCIENCE & POLICY GROUP

The Sabin-Aspen Vaccine Science & Policy Group brings together senior leaders across many disciplines to examine some of the most challenging vaccine-related issues and drive impactful change. Members are influential, creative, out-of-the-box thinkers who vigorously probe a single topic each year and develop actionable recommendations to advance innovative ideas for the development, distribution and use of vaccines, as well as evidence-based and cost-effective approaches to immunization.

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We have the honor of presenting the third annual report of the Sabin-Aspen Vaccine Science & Policy Group, *Powering Vaccine R&D: Opportunities for Transformation*, at an extraordinary moment in history. COVID-19 has demonstrated as never before that an efficient, science-based system to move safe and effective vaccines through the pipeline is absolutely vital to global well-being. The big ideas presented in this volume are designed to advance that goal — not only for pandemics but also for the many other infectious diseases that threaten our health.

A stellar group of experts has gathered together to think about how best to move forward. The Sabin-Aspen Vaccine Science & Policy Group is co-chaired by Harvey V. Fineberg, president of the Gordon and Betty Moore Foundation, and Shirley M. Tilghman, president emerita of the university and professor of molecular biology and public affairs at Princeton University. They are joined by an accomplished group of 22 leaders whose careers span numerous fields and disciplines. Some bring a deep well of knowledge in vaccinology; others offer insights from the sciences, public health, finance, ethics, journalism and elsewhere. Collectively, they represent the public, private, philanthropic and advocacy sectors. We owe a debt of gratitude to Wellcome Trust and the Bill & Melinda Gates Foundation for giving us the means to bring these influencers together.

Each of us, the signatories of this letter, is grateful to the other as well. In the three years since the Vaccine Science & Policy Group began to convene, the Sabin Vaccine Institute and the Aspen Institute have proven to be natural allies. Our skill sets are complementary and synergistic. Sabin, with its storied history of championing vaccine science and equitable worldwide access to immunization, and Aspen, with its widely recognized convening power, are partners in an enterprise we both believe can help transform global health.

As the vaccine group presents this report, we are confident that the partnership it represents will continue to influence dialogue, policy and action. The two prior reports, *Accelerating the Development of a Universal Influenza Vaccine* and *Meeting the Challenges of Vaccination Hesitancy*, endure to inform and inspire, and we believe that *Powering Vaccine R&D: Opportunities for Transformation* will do so as well.

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FOREWORD

The release of this report, *Powering Vaccine R&D: Opportunities for Transformation*, by the Sabin-Aspen Vaccine Science & Policy Group coincides with a monumental achievement — the rollout of immunizations aimed at curbing the spread of COVID-19 across the globe. Faced with the most devastating pandemic in a century, the scientific community built on a decade of prior research to bring vaccines into use in record time. That is both a cause for celebration and an impetus to develop more and better vaccines for both pandemic and endemic infectious diseases.

Future pandemics loom, and many endemic diseases cost hundreds of thousands of lives every year. Diseases such as tuberculosis, HIV and malaria are among the top 10 killers in low-income countries, while Ebola, Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS-1) and Zika continue to roam the planet, with the potential to spiral out of control. While we cannot predict precisely which other pathogens will emerge in the coming years, we can be confident that they will indeed emerge.

When the Vaccine Science & Policy Group decided to study the R&D component of the vaccine/vaccination ecosystem, SARS-CoV-2 was an unknown virus. Even so, we understood the urgency of more streamlined and efficient R&D — the many steps that bring a vaccine from design to animal and human testing and on to regulatory approval and manufacturing.

COVID-19 informed our thinking, of course, but this report examines many disease-causing pathogens in considering the need for vaccines. Our goal is to glean important lessons about what has worked well in the past, and where systemic gaps remain.

As co-chairs of the vaccine group, it has been our privilege to guide a diverse, interdisciplinary group of innovators. Together, we took a deep dive into the influences and challenges that shape vaccine R&D, aiming to strengthen this crucial feature of the vaccine/vaccination ecosystem. As we have done for the past three years, we began our deliberations by commissioning a package of background papers that provide context. The group then gathered for two and a half hard-working days of collegial discussion, interspersed with expert presentations.

Together, we took a deep dive into the influences and challenges that shape vaccine R&D, aiming to strengthen this crucial feature of the vaccine/vaccination ecosystem.

This year, we met virtually for the first time, and while we missed the in-person dynamics and beautiful setting of the Aspen Institute campus, our conversations were robust and productive. Based on these in-depth exchanges, we agreed on five big ideas and present them in the consensus paper that opens this report. These underscore the importance of an effective leadership structure and the imperative of vaccine science, and call for reimagined clinical trials, a restructured approach to regulatory science and incentives to align the priorities of the many players who engage with vaccine R&D.

Several valuable background papers informed the consensus document and are included in this report:

- *Understanding the Vaccine Ecosystem: Structure and Challenges*, by Stefano Malvolti and Karyn Feiden
- *Designing an R&D Preparedness and Response Ecosystem for Potentially Pandemic Pathogens*, by Nichole Lurie and Gerald T. Keusch
- *Understanding Global Vaccine Economics and Research and Development*, by Jennifer Shulman, Rowena Ahsan and Kayleigh O'Malley
- *The R&D Response to COVID-19: What Can We Learn for the Vaccine Ecosystem*, by Anis Chagar, Michael Thomas, Linda Zuo and Mike Watson

As with the group's two previous reports — one exploring strategies for developing a universal influenza vaccine, the other taking aim at vaccination hesitancy — we understand that advancing bold ideas about vaccine R&D is only a first step. Our members are part of influential networks who are prepared to turn these ideas into strategies that will propel them forward. The Sabin Vaccine Institute has been driving progress against vaccine-preventable diseases for decades, and the Aspen Institute has a proud tradition of promoting dialogue on some of the planet's thorniest challenges. Together, this partnership ensures that our reports garner attention, advocates and action.

Finally, no introduction would be complete without offering the most sincere thanks to the members of the Sabin-Aspen Vaccine Science & Policy Group, who give so generously of their time; to the Sabin Vaccine Institute and the Aspen Institute, whose partnership and dedicated staff have given us a home; and especially to Wellcome Trust and the Bill & Melinda Gates Foundation, whose generous support makes this report possible. Together, we are taking strides toward a vaccine R&D system that can produce more vaccines, more rapidly, and reduce the burden of disease in the world.

Harvey V. Fineberg, M.D., Ph.D.
Co-chair

Shirley M. Tilghman, Ph.D.
Co-chair

Part 1

SABIN-ASPEN VACCINE SCIENCE & POLICY GROUP REPORT

Powering Vaccine R&D:
Opportunities for Transformation

EXECUTIVE SUMMARY

When the Sabin-Aspen Vaccine Science & Policy Group decided in 2019 to consider ways to improve the research and development (R&D) component of the vaccine/vaccination ecosystem, SARS-CoV-2 (formally, severe acute respiratory syndrome coronavirus 2) was an unknown virus, and the word COVID-19, the disease it causes, had yet to be coined. While the subsequent pandemic made vaccine R&D appear to have been a prescient choice for the group's annual meeting and report, we had initially chosen the topic to expand on our first report, *Accelerating the Development of a Universal Influenza Vaccine*, which focused on a single vaccine (Sabin-Aspen Vaccine Science & Policy Group, 2019).

As SARS-CoV-2 spread, the group retooled to ensure that we learned as much as possible from the unfolding pandemic, the historic pace of the response and the revolutionary technologies that were put to such swift use to combat it. Recognizing the imperative to be better prepared for the next such crisis, we also saw a crucial need to draw on experiences with prior and ongoing vaccine R&D for emerging diseases such as Ebola and Zika; to consider perennial challenges, such as influenza, malaria, tuberculosis (TB) and human immunodeficiency virus (HIV); and to ponder needed improvements on some existing vaccines, such as pertussis. There are both similarities and significant differences in the nature of these threats and how they need to be addressed, but each has something to teach us about the strengths and flaws in the current R&D enterprise — and the path forward.

CALL TO ACTION

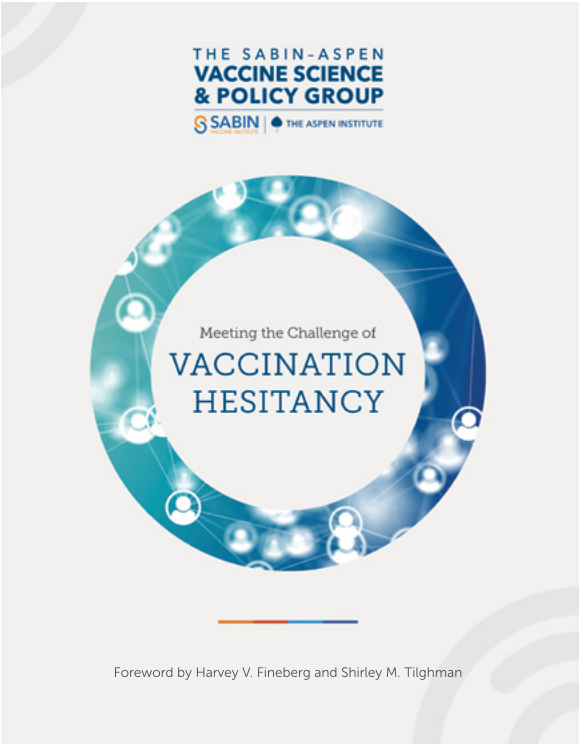
As we learn the lessons from the past, we expect to see opportunities to overhaul current practices in time for the next pandemic, whenever it may strike; to make strides against the many endemic diseases that remain without adequate vaccines; and to accelerate the development of next-generation vaccines that improve performance or facilitate access and demand. All of that responds to the warning that infectious diseases have repeatedly sounded: do not neglect us.

With novel scientific tools and technologies opening new pathways for vaccines, and a recognition that equity in the R&D process must be as much of a priority as equity at the last mile, our work is very much of the moment. A brief look back also lends perspective to the ultimate purpose of the vaccine enterprise. Vaccines are one of the top 10 public health achievements of the 20th century, according to the U.S. Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 1999), and what the World Health Organization (WHO) calls a "global health and development success story" (WHO, n.d.-d). A critical bulwark against infections, the value of vaccines is never clearer to people or governments than during pandemics, as COVID-19 clearly demonstrates.

> As we learn the lessons from the past, we expect to see opportunities to overhaul current practices in time for the next pandemic, whenever it may strike.

On another hopeful note, pandemics can be powerful stimuli for innovation. U.S. government investments in vaccines and other infectious disease research following the influenza pandemic of 1918-19 contributed to a twenty-twofold reduction in deaths from diseases among U.S. troops in World War II compared to World War I (Bush, 1945). The military-funded research also laid the groundwork for the postwar development of vaccines against the viruses that cause yellow fever, polio, measles, rubella and hepatitis A and B (Duffy, 1992, pp. 270–279). Efforts by the WHO and other global institutions to ensure routine vaccination around the world helped to end smallpox, nearly eradicate polio and avoid more than 2 million to 3 million deaths each year from other vaccine-preventable illnesses (WHO, 2020b).

Increasingly, deploying vaccines against infectious diseases faces a new challenge — vaccination hesitancy, reflecting a breakdown in trust that has led to delayed vaccination or the refusal to receive them. The urgency of research into this last mile challenge — since vaccinations, not vaccines, prevent disease — was also a focus for the group, which spent a



year of study before issuing its 2020 report, *Meeting the Challenge of Vaccination Hesitancy* (Sabin-Aspen Vaccine Science & Policy Group, 2020). Our return to R&D in this report reflects our continuing commitment to the end-to-end thinking that we believe is key to progress.

Vaccines and vaccinations are the two subsystems of a complex ecosystem, each with its own set of characteristics. The vaccine subsystem starts with the basic science that makes it possible for R&D processes to move forward and continues along a pathway that propels a product from the lab to approval for clinical use, commercial-scale manufacturing, and distribution, as well as the policies that govern these practices. Vaccination is the process of actually getting vaccines into human bodies, including the delivery and administration of the product, the willingness of individuals to be inoculated and the programs and policies that facilitate these steps.

The group's decision to focus on R&D in 2020 reflected, in part, broad concerns about the declining number of vaccine developers (Danzon & Pereira, 2005; Wilsdon et al., 2020) and the structural failures that have slowed the arrival of new and improved vaccines. But those challenges stand beside remarkable accomplishments in recent years, including the new platforms that have enabled the rapid response to SARS-CoV-2. The arrival of several authorized vaccines less than a year after the virus was identified in December 2019 demonstrates the speed that is possible when we galvanize and align scientific capabilities with the necessary policymaking and financial resources. Timely data sharing, "real-time" publication and heightened collaboration across disciplines, sectors and borders were also essential contributors to the unprecedented pace of development.

The question is how those and other key elements of the accelerated process can be assembled, solidified, improved and applied to produce other needed vaccines — and then institutionalized so they are pandemic-ready. Malaria, TB and HIV remain among the top 10 causes of death in low-income countries (WHO, 2020c). And numerous other endemic infections, including Ebola, influenza, Middle East Respiratory Syndrome (MERS), Nipah virus and Zika, demand attention because they also pose significant risks to local populations and could seed future pandemics. While not all of the emergency measures used for SARS-CoV-2 need to or should be employed in every case, attention to restructuring R&D to produce essential vaccines for the infectious diseases we already recognize, and for those yet to emerge or be discovered, is imperative.

In that spirit, five key themes shaped the deliberations of the group:

- Developing and having timely access to safe and effective vaccines for all people is a moral imperative
- The devastation wrought by COVID-19 demands that we revisit and restructure the vaccine R&D enterprise
- Scientific breakthroughs and new technology expand ideas of what is possible
- A top-down, bottom-up approach, guided by coordinated leadership at all levels, advances vaccine R&D most effectively
- Public confidence in the R&D process is imperative to the ultimate goal of reducing the toll of vaccine-preventable diseases

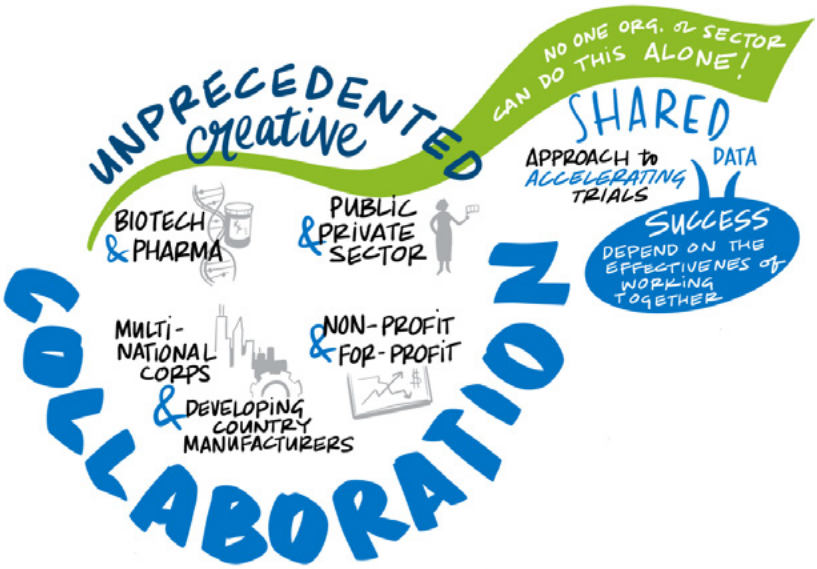
FIVE BIG IDEAS TO POWER VACCINE R&D

The Sabin-Aspen Vaccine Science & Policy Group developed a package of five big ideas, summarized below, that we believe will engender a more efficient and responsive approach to vaccine R&D. The context for these ideas is detailed in the report that follows, which concludes by elaborating on each of them.

Define leadership roles, responsibilities and mechanisms of accountability to prepare for the R&D demands that surface in a pandemic. The global organizations that now have core roles to play in vaccine R&D need to map out real-time vaccine preparedness and response strategies so that they are ready to act as infectious diseases emerge or spread. Their leaders

should convene in a structured setting to develop advance plans designed to surface key issues that need to be addressed and to make decisions about who will be responsible for taking them on, recognizing the imperatives of equity, clear communication and adequate capacity. A truly global consensus on how to move forward will require a multicentric leadership model that engages partners not only in the United States and Europe but also in China, Brazil, India and the African nations.

Propel a transdisciplinary research effort built around partnerships to expand and advance vaccine science. Nothing in recent times has showcased the payoff of basic science investment as much as vaccines to curb COVID-19. The vaccines are also a testament to the power of partnerships to break down institutional and competitive barriers to scientific collaboration. Such success can only become routine with intentional efforts to bring people together across fields in an environment designed to stimulate creative problem-solving and drive novel research and transformational science. To promote convergence, the group recommends support for a research infrastructure that creates opportunities for novel approaches and risk-taking; leverages lessons from adjacent scientific areas, ranging from the chemistry and physics of vaccine formulation to the immunologic basis of protection; and creates two-way learning opportunities between research focused on pandemics and on long-standing endemic diseases.



Reimagine clinical trials. Clinical trial design is ripe for more efficient and nimbler approaches. From the earliest design stage, clinical trials should consider the programmatic and policy questions likely to arise following vaccine authorization or approval. Equity and efficiency must also be prime drivers, with lower- and middle-income countries as full partners in clinical trial development at every stage. Bringing together large datasets and analyses of clinical and laboratory information on infected and vaccinated individuals may make it possible to identify immune correlates of protection, allowing regulatory approval to

be based on smaller and faster trials. For example, the use of master protocols can accelerate trials and make findings easier to compare. Global networks of clinical trial sites and adaptive trial designs can speed data-gathering and postmarketing surveillance; a genuine commitment to advancing vaccine safety science is also key.

Restructure regulatory science to reflect advances in vaccine R&D. Transformative vaccine discoveries and technology must be accompanied by equally transformative approaches to regulatory science and process. Without compromising safety and efficacy, regulatory innovations should be pursued to streamline preclinical evaluation; make vaccine trials faster, nimbler and more cost-effective; and enhance product scale-up and manufacturing to improve global access. Harmonizing global regulatory standards and developing training opportunities, technical assistance and resource mobilization are key to strengthening and extending regulatory capacity, especially in lower- and middle-income countries.

> Transformative vaccine discoveries and technology must be accompanied by equally transformative approaches to regulatory science and process.

Importantly, some changes may apply only to vaccines in emergency situations. For example, it may be appropriate to consider process improvements in the U.S. Food and Drug Administration (FDA)'s Emergency Use Authorization (FDA, 2021), the rolling reviews permitted by the European Medicines Agency to assess data as they become available (European Commission, 2020), and the WHO's Emergency Use Listing procedure (WHO, n.d.-b). Other changes will apply across the board.

Position vaccines as a public good and align incentives so that benefits accrue to all sectors of society. Building on the recognition that the public has an interest in safe and effective vaccines and that companies expect to be rewarded for producing them, the incentives that drive action need to be examined in order to align them more closely. Agreeing on the research agenda is a front-and-center goal so that manufacturers, researchers and other core partners can be incentivized to pursue vaccine R&D that takes aim at the greatest threats to the global community. There should also be a strong push to develop or maintain policies and practices that promote information sharing. To guide alignment, criteria are needed to help determine which incentives should be offered and under what circumstances.

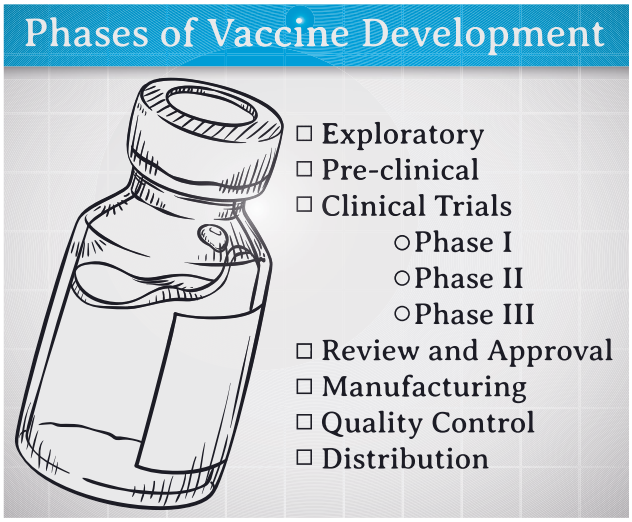
POWERING VACCINE R&D: OPPORTUNITIES FOR TRANSFORMATION

PRIMER ON THE R&D COMPONENT OF THE VACCINE/ VACCINATION ECOSYSTEM

Vaccine R&D is the starting point for successfully generating any new vaccine, which traditionally has taken years or even decades to complete because of the rigors of the testing process and the complexity of regulatory approval. Many vaccines never get much beyond the conceptual stage, while others fail somewhere further along the development pathway (Dumonteil et al., 2019).

A Web of Activities

Like natural ecosystems, the R&D component of the vaccine/vaccination ecosystem is a complex and dynamic network with many distinct parts:



- *Discovery and scientific research* take place in the laboratory and generate the pharmaceutical product to be studied
- During *preclinical research*, candidate vaccines are developed and tested in animals to assess basic safety and immunogenicity before they are evaluated in human beings
- *Three phases of clinical testing* establish vaccine dosage and scheduling regimen and gather safety, immunogenicity and efficacy data in increasingly larger populations
- *Scale-up and large-scale manufacturing* consistently producing the needed volume of vaccines
- *Regulatory submission and approval* allows the product to come to market

These processes vary considerably by country and are intended to ensure that a product meets safety and efficacy standards before it is released for public use*.

Note that the entire vaccine/vaccination ecosystem has other components that need to work together seamlessly for optimal performance. To name just a few, more effective global surveillance and genomic sequencing capacity are priorities to ensure rapid response before a pathogen engenders a pandemic. Further along the continuum, distributed manufacturing capacity, especially for newer-platform vaccines, is essential to ensure global availability. Other value-added opportunities include improved storage strategies and better technologies for deployment and administration — the last inch of the last mile. The Sabin-Aspen Vaccine Science & Policy Group supports heightened attention to these and other issues, but they are not the subject of this report.

The three phases of clinical testing that are generally required for regulatory approval have historically occurred sequentially, but the accelerated development of COVID-19 vaccines has shown that these processes can operate in parallel without sacrificing safety and immunogenicity assessments when the need is urgent.

- *Phase 1* tests a promising vaccine in a small number of healthy volunteers to assess safety and immunogenicity
- *Phase 2* engages several hundred volunteers and expands the numbers for safety signals while beginning to assess how well various dosages and regimens of the vaccine generate an immune system response in more study subjects and different populations
- *Phase 3*, the last step before filing for regulatory approval, engages thousands of volunteers with the primary goal of determining whether the vaccine prevents infection or the disease it causes (FDA, 2020)

In addition to establishing a vaccine's safety and efficacy, developers must provide evidence that adequate process controls will be in place during manufacturing to ensure consistency.

* This consensus framework definition was circulated to the Sabin-Aspen Vaccine Science & Policy Group to guide its discussions, but it is not an officially or universally recognized definition.

Each part of the R&D process involves its own web of activities that differ around the globe, influenced by diverse sets of actors, regional priorities, health systems, infrastructure capacity, political undercurrents and cultural norms and beliefs. High costs, the challenges of recruiting an adequately representative population, and retaining participants through the duration of a clinical trial are frequent barriers to gathering critical data and completing trials in a timely fashion. Given the many steps involved, a manufacturer will generally not begin to produce a vaccine at volume until success is in sight and regulatory approval is assured. With SARS-CoV-2, however, the government accelerated vaccine development and availability with direct financial support and advance market commitments, incentivizing manufacturers to begin at-scale production prior to completing efficacy trials and long before final regulatory approval without assuming financial risk.

A Network of Players

Vaccine R&D involves researchers, funders, developers, manufacturers, purchasers, payers, regulators, policy makers and program implementers, each influenced to varying degrees by disease burden, technical feasibility, opportunity cost and other factors. There is also the crucial need for ongoing engagement at the community level, beginning at the earliest stages of the R&D process and always with the end user in mind.

The players interact in multiple ways and for a variety of purposes, sometimes contractually and sometimes through other formal or informal collaborations. The research effort, for example, occurs within academic settings and university-affiliated teaching and research hospitals; in government-run laboratories at the National Institutes of Health (NIH) in the United States and similar institutions in Europe, China, India, Russia, Brazil, Cuba, Indonesia, South Korea and elsewhere; in contract research organizations that often have public funding; in major multinational pharmaceutical corporations and other large-scale vaccine producers; and in small biotech companies.

Within the United States, the NIH supports and conducts research across the scientific spectrum, spanning studies in molecular pathogenesis and basic immunology through the clinical testing of candidate vaccines (National Institute of Allergy and Infectious Diseases, 2020). Decades of core support from the NIH and other federal agencies, notably the Department of Defense, yielded the messenger RNA (mRNA) platform technology behind the first two authorized COVID-19 vaccines (Allen, 2020), a compelling testament to the contributions of basic science to vaccine innovation. This commitment to early research and the sorting-out process that is often used to identify and promote encouraging approaches have also lessened the risk of failure for vaccine developers, increasing the odds that they are pursuing more promising candidates.

Established in 2006, the Biomedical Advanced Research and Development Authority (BARDA), under the jurisdiction of the U.S. Department of Health and Human Services, is also a major funder of pandemic vaccine R&D, one focus within its broader mission of safeguarding the nation from potential chemical, biological, radiological and nuclear threats. BARDA was a primary funder of the COVID-19 vaccine jointly developed by NIH and Moderna, which received emergency use authorization from the FDA in December 2020, as well as other COVID-19 vaccines and some of the diagnostic and therapeutic tools in the COVID-19 arsenal (BARDA, 2021).

Another key player in vaccine R&D is the Coalition for Epidemic Preparedness Innovations (CEPI), launched in 2017 with a mission "to accelerate the development of vaccines against

emerging infectious diseases and enable equitable access to those vaccines for people during outbreaks" (CEPI, n.d.). A global public-private partnership, CEPI works on many levels to drive forward the development and deployment of new vaccines. Key activities include stockpiling investigational vaccines with an established safety profile, funding innovative platform technologies to accelerate vaccine development and manufacture when a new pathogen is identified, strengthening response capacity in countries at risk, and advancing regulatory science.

In the United States, vaccines are reviewed and licensed by the Center for Biologics Evaluation and Research within the FDA. Other key regulatory authorities around the globe are the European Medicines Agency, Japan's Pharmaceuticals and Medical Devices Agency, Health Canada and Australia's Therapeutic Goods Administration, each with its own approach to making products available in public health emergencies. Lower- and middle-income countries may not have the capacity to provide rapid expert reviews of novel vaccines and typically rely on evaluations by agencies in other countries. The inefficiencies that come from a lack of harmonized standards for ensuring product safety, efficacy and quality, and the dictates of labeling and packaging, often force developers to meet inconsistent local requirements, and sometimes to conduct additional clinical trials in order to receive regulatory approval (Malvolti & Feiden, 2021).

The WHO, which works at many levels to increase access to vaccines around the world, has tried to ease this problem by coordinating vaccine approvals internationally through its Prequalification Program (WHO, n.d.-c). Established in 2001, the program created a standardized procedure for assessing the quality, safety and efficacy of candidate vaccines (as well as other pharmaceuticals) as a means of supporting and strengthening the capacity of regulatory systems worldwide (Coyne, 2019). The WHO also employs the Emergency Use Listing procedure to assess the suitability of vaccines, therapeutics and diagnostics during public health emergencies. By sharing that information with national regulatory authorities, the WHO enables products to be swiftly authorized for use in countries that have limited resources to conduct their own evaluations (WHO, n.d.-b).

The WHO's activities fit within a broader equity agenda. Realizing the goals of that agenda requires establishing equity as a core principle and committing to community ownership at every stage of trial design by engaging local researchers from the outset and developing global clinical trial networks that include populations diverse by ethnicity, gender and age. In that context, regional efforts are essential to ensure that lower- and middle-income countries are full partners in the development of vaccines that their populations will ultimately use. The Africa Centres for Disease Control and Prevention Consortium for COVID-19 Vaccine Clinical Trials (CONCVACT), for example, was launched in July 2020 by the African Union Commission to support testing, approval and access to COVID-19 vaccines in Africa (Africa Centres for Disease Control and Prevention, 2020).

A number of other players have pivotal roles in vaccine procurement and dissemination. While these are separate components of the vaccine/vaccination ecosystem, their work merits mention because they can offer incentives that influence the R&D process — such as advance market commitments for vaccines that meet certain performance criteria.

Gavi, the Vaccine Alliance, provides support for vaccines against 17 infectious diseases, with the goal of increasing access to new and underutilized vaccines in lower- and middle-income countries. Established in 2000 with the WHO, UNICEF, the World Bank and the Bill & Melinda Gates Foundation as core partners, Gavi links donors, national governments, civil society organizations, the pharmaceutical industry, research and technical institutes and others to make high-volume, low-price vaccines widely available (Gavi, the Vaccine Alliance, n.d.). Now the largest vaccine funder in the world, Gavi has unquestionably achieved many of its access goals, but some have questioned whether its pooled procurement and market-shaping activities have put pressure on vaccine prices, posing a potential threat to the industry's sustainability and capacity to innovate (Watson & Faron de Goer, 2016).

The recognition of the critical need for global coordination in the vaccine response to COVID-19 led to the establishment of COVAX, the vaccine pillar of the Access to Covid Tools Accelerator (ACT-A) (WHO, n.d.-a), which is co chaired by Gavi, CEPI and the WHO. COVAX is

a platform to support the research, development and manufacturing of COVID-19 vaccines; negotiate their pricing; allocate the supply through a formula designed to provide equitable global access regardless of a country's income level; and support the introduction and rollout of authorized vaccines. The COVAX Facility, the global risk-sharing mechanism for pooled procurement and equitable vaccine distribution, has secured the participation of 191 economies that are either eligible to receive doses or are funding contributors (WHO, 2020d). China joined the COVAX Facility as a procuring participant somewhat after it was initially established, and the United States announced it would contribute funding after President Joe Biden took office, leaving Russia as the only high-income country as of March 2021 that has not opted to participate.

Despite the sophistication and vast reach of the vaccine/vaccination ecosystem, lack of coordination remains one of its enduring characteristics. In a background paper prepared for the group's meeting, two authors involved in the COVID-19 response laid out the R&D gaps that exist (Lurie & Keusch, 2021). Funders and research groups, they write, were part of a "conductorless orchestra[.] [E]ach ... played its part, often exceedingly well, but not always in a way to support an ideal tempo or harmony, or to eliminate needless repetition of movements." In particular, they point to the lack of predetermined strategies to undertake and share the early enabling scientific data, support the manufacturing of billions of vaccine doses, and guide an equitable, global distribution system. To overcome these gaps, the authors propose the elements of an end-to-end R&D Preparedness and Response Ecosystem.

Despite the sophistication and vast reach of the vaccine/vaccination ecosystem, lack of coordination remains one of its enduring characteristics.

HIGHLIGHTS OF VACCINE SCIENCE

The R&D that is speeding COVID-19 vaccines through the vaccine/vaccination ecosystem has been years in the making. The technologies in play were launched from a solid base of prior innovation and research investments in a broad array of fields, including structural biology, immunology, virology, oncology, genomics and informatics. Experts across a wide range of disciplines, many without prior training in vaccinology, helped push vaccine development forward, an encouraging sign in a field that has historically been siloed from other areas of research. New vaccine technologies have also benefited from ongoing pandemic preparedness research programs. An example of this innovation is BARDA's support since 2007 of platforms that use cell cultures and recombinant approaches rather

than the more traditional chicken eggs to make seasonal influenza vaccines (Elvidge, 2016). The quest to develop next-generation vaccine production platforms is now being deployed to make COVID-19 vaccines.

Vaccines are highly complex products in no small measure because they generally derive from biological source material, including microorganisms and cellular derivatives, which must be carefully characterized, tested and standardized.

These biological materials must be processed and formulated in specialized manufacturing facilities that have met rigorous quality-control standards. In the United States, the FDA requires product characterization data that include a lot-release protocol identifying the tests that manufacturers must conduct on each batch of vaccines to ensure reliably consistent quality on a lot-by-lot basis (FDA, 2020).

About two-thirds of the vaccines in the COVID-19 pipeline use established technologies, including protein subunit vaccines, replicating and nonreplicating viral vectors and inactivated viruses (Chagar et al., 2021). The remainder use newer technologies that could result in "plug and play" platforms employable against multiple pathogens in the future, such as mRNA and adenovirus vectors, which were pioneered in part from therapeutic drug research programs.

Since its discovery in 1961, mRNA has offered tantalizing promise as a new class of therapy, especially for cancer (Sahin et al., 2014). When used in vaccines directed against SARS-CoV-2, mRNA works by instructing the cells to make a harmless piece of the spike protein found on the surface of the virus. The body generates an immune response to that protein, preventing the virus from infecting human cells. Adenovirus vectors likewise stimulate an immune response, in this case by using a nonreplicating viral vector to deliver the genetic code for the spike protein into cells so that the body can learn to attack it. The adenovirus vector technology has previously been licensed in an Ebola vaccine (European Medicines Agency, 2020).

Both the mRNA and adenovirus approaches to vaccine development had been studied on other emerging viruses, including Zika and MERS, as part of preparedness projects. Funding from the U.S. Department of Defense, BARDA, the NIH, the United Kingdom and CEPI were all key to developing the technologies used in the new vaccines (Hatchett, 2020). The early success of these platforms, as indicated by their safety and efficacy, suggests that future vaccine development efforts may increasingly rely on them because their flexibility allows a working vaccine to be produced based on an organism's genetic code, offering unprecedented speed and precision.

Whatever the technology, continued scientific progress depends on attracting more investments in vaccines to combat both pandemic and endemic pathogens. Large-scale Phase 3 trials, while still the norm, can be an impediment to that goal because they are costly and time consuming, and no predictable system exists for financing them. Investments in HIV, oncology and immunology have all suggested alternative testing approaches and offer learnings of interest about the potential use of biomarkers and surrogate endpoints that can generate information about efficacy more efficiently without sacrificing standards.

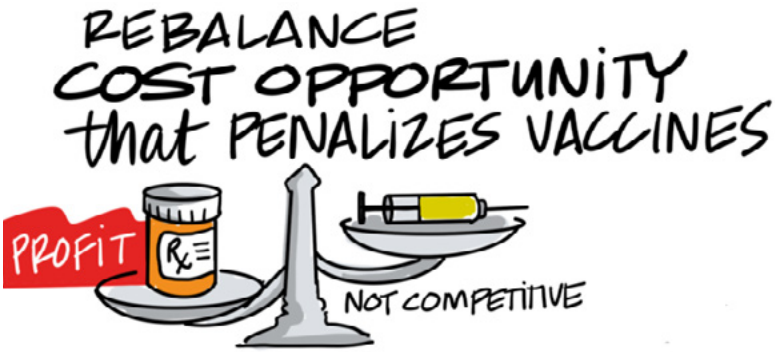
Establishing immunologic correlates of protection could reduce the size and complexity of conducting clinical trials and dramatically lower vaccine development costs and speed regulatory approvals, potentially enhancing commercial appeal for both first-wave vaccine developers and subsequent market entrants. The hope is that making the search for these

correlates a priority, and sharing the large datasets and analyses of clinical and laboratory information from COVID-19-infected patients and vaccinated individuals across vaccine development programs, will help to identify novel biomarkers that predict protection. COVID-19 has also highlighted the urgent need to accelerate research efforts on the breadth of host responses to vaccines, including the structure and function of antibodies and other protective components of the immune system.

Even where the nature of the immune correlates are unclear, regulators may be able to accept clinical trial evidence of immune responses that bridge to those of other vaccines. For example, once a given mRNA vaccine demonstrates its ability to prevent COVID-19, regulators could theoretically approve subsequent vaccines that use the same platform if they demonstrate the same immune responses. Such an accelerated pathway will become increasingly important as new viral mutations emerge. That kind of scientific innovation could also incentivize broader participation in vaccine R&D.

VACCINE DEVELOPMENT CHALLENGES AND INCENTIVES

Traditionally, the global pharmaceutical industry has favored products designed to treat disease, rather than to prevent it, since the former typically require multiple doses, are used for longer periods of time and are more likely to produce high returns on their investments. Until recently, vaccines have not produced similar largesse, in part because they are primarily used by a limited pediatric population and provide needed protection with few doses. That often puts public health at odds with the profits and sustainable business model required by many of the players in vaccine R&D. The remarkable market potential engendered by the COVID-19 pandemic — with billions of people needing vaccines now and perhaps boosters later to maintain immunity and protect against emerging variants — could change this equation, at least for some diseases.



To a for-profit enterprise, the relative disadvantages of investing in vaccines rather than in blockbuster drugs are many, accounting for the dramatic consolidation of the vaccine market since the 1970s (Xue & Ouellette, 2020). Along with their more limited use, vaccines are held to the highest safety standards since they are administered to healthy people, especially

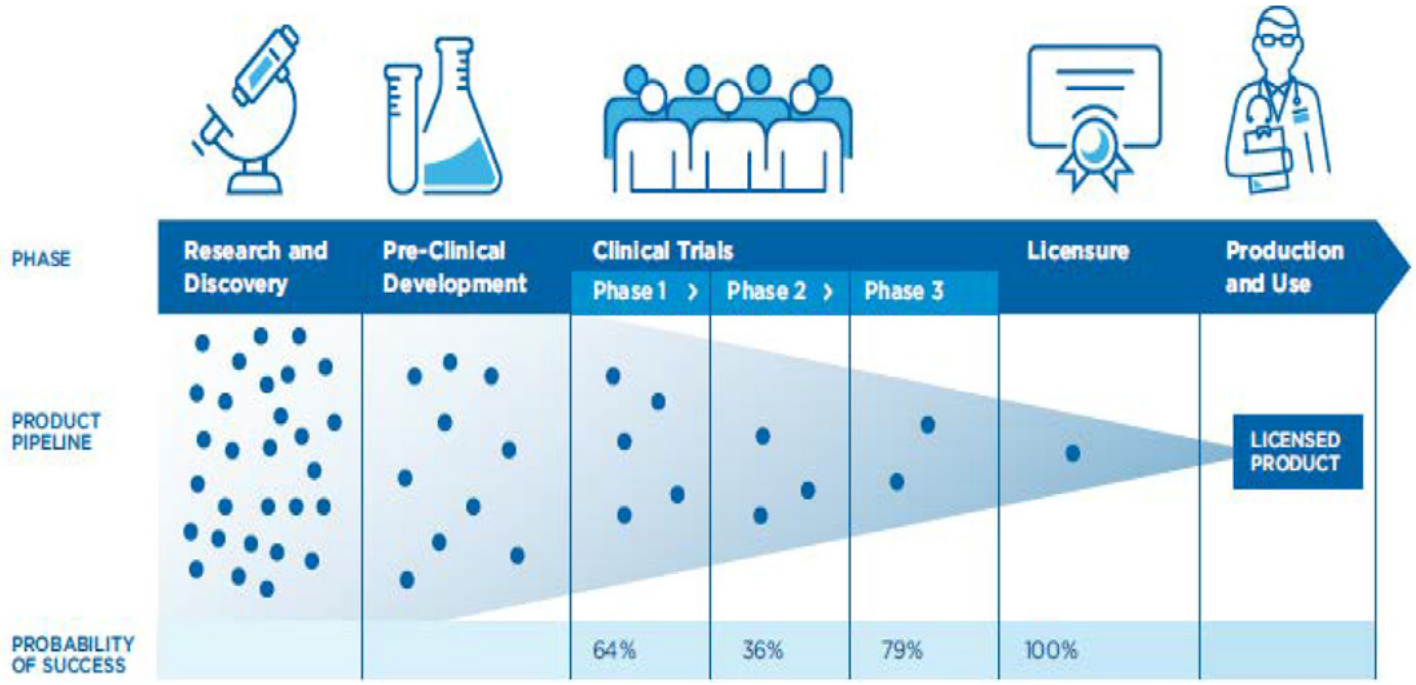
healthy infants and children. Effective drugs for serious diseases with limited therapeutic options, by contrast, can sometimes be successfully marketed even when they carry significant risks of a serious side effect.

Moreover, the complexity of the manufacturing process generally makes it necessary to build a new plant for each vaccine. That process can take five years and cost at least $350 million in the United States and $150 million in India (M. Watson, personal communication, November 8, 2020), risks that discourage companies from building a plant until efficacy has been documented in completed clinical trials. Here, too, the new generation of viral vector and mRNA vaccines may change the equation, possibly making it viable to use a single plant to manufacture multiple vaccines.

The barriers to R&D are suggested by an analysis initially performed for the Wellcome Trust that identified 54 challenges, including 16 priority challenges (see Table 2 in Malvolti & Feiden paper, this volume), preventing worthy vaccine candidates from progressing from Phase 2 clinical testing through licensure. Among these challenges are the lack of recognized surrogates or correlates of efficacy, limited regulatory support for adaptive clinical trial design, the lack of harmonized requirements across regulatory agencies, the long lead time needed to establish significant manufacturing capacity, and the lack of partners to receive technology transfer. Pressure from governments and nongovernmental organizations (NGOs) to control price also takes its toll, with the opportunity cost of vaccine development sometimes too high to attract investors who have more potentially profitable options in other diseases and therapeutics, such as diabetes, the chronic diseases of aging and immuno-oncology drugs. Competing pressures on scientific capacity within a company are a further limitation.

While there has been some improvement in predictive capacity along the R&D continuum from animal studies to licensure, discrepancies between immunologic results and determination of efficacy in costly and complex Phase 3 clinical trials can also be stumbling blocks, suggesting the risk of undue reliance on early studies (FDA, 2017) (Figure 1).

Figure 1. Probability of success across phases of vaccine development



Source: Biotechnology Innovation Organization; BioMedTracker; Amplion. Clinical Development Success Rates 2006-2015.

Despite these barriers, the vaccine market for the four largest (by value) multinational vaccine producers — GlaxoSmithKline, Merck, Pfizer and Sanofi — has grown sixfold over the past two decades. By comparison, the market for anti-infectives exclusive of vaccines has slightly more than doubled, while the market for oncology drugs has increased thirteenfold (EvaluatePharma, 2021).

Investment Priorities and Procurement Strategies

A background paper drawn from Wellcome Trust research and prepared for the Sabin-Aspen Vaccine Science & Policy Group reviews the many influences on vaccine investment targets, sorting them into the broad categories of technical feasibility, unmet medical need, value creation and strategic fit (Malvolti & Feiden, 2021). While the significance of each factor varies depending on the phase of development and the type of developer, the misalignment between financial incentives and public health needs is often striking.

That is particularly reflected in the disproportionate concentration of vaccine R&D in high-income countries, where four-fifths of the dollar value of the global vaccine market is generated, despite accounting for only one-fifth of the annual volume of vaccines consumed

(Shulman et al., 2021). Multinational corporations have generally pursued high-margin vaccines, which are marketed at a relatively low volume and designed to prevent diseases with relatively less global impact on morbidity and mortality, such as an updated pediatric pneumonia vaccine (Malvolti & Feiden, 2021).

The result is that investment priorities have historically skewed away from endemic diseases that pose their most intense threats to lower- and middle-income populations. For example, a dearth of capital investment has discouraged vaccine R&D to combat malaria and TB. The Ebola virus was well recognized before its aggressive spread, but earlier isolated outbreaks in impoverished regions had never received attention from vaccine developers because the market was limited and the return on investment was expected to be low. The Zika virus, too, had been discovered decades earlier, but the complication of microcephaly in infants born to infected mothers was unknown, and the generally mild forms of the disease from Africa and Asia had not pushed it up the priority list (Billington et al., 2020).

In recent years, the bias against investing in vaccines with large markets but low profit margins has begun to shift as governments, the Bill & Melinda Gates Foundation and Gavi develop strategies to incentivize vaccine R&D and the demand for vaccines. Their combined efforts have helped to increase the number of companies producing basic vaccines for low-income countries from five in 2000 to 18 in 2020 (J. Weintraub, personal communication, November 9, 2020).

The companies within the Developing Countries Vaccine Manufacturing Network (DCVMN) provide another source for R&D and manufacturing capacity. The alliance has brought together some 41 manufacturers from 14 countries and territories, primarily in Asia, Latin America and Africa, which produce vaccines for large, local markets at low prices. DCVMN manufacturers now supply more than 40 different types of vaccines (DCVMN, n.d.). Unlike multinationals, participating companies rely heavily on grants, loans and other funding from public and philanthropic sources. The importance of this effort is reflected in data showing

that DCVMN supplies at least half the vaccine doses procured by Gavi and UNICEF in recent years from a variety of manufacturers with a wide range of capacity (Hayman & Pagliusi, 2020).

The pooled procurement mechanisms these and other multilateral agencies employ have proven to be important tools for increasing access to vaccines by generating the volume necessary to attract manufacturers. While some researchers have suggested that the downward pricing pressure they exert on vaccines could ultimately drive manufacturers out of lower- and middle-income markets (Shulman et al., 2021), affordability remains essential to meeting global needs.

Power of Partnerships

The partnerships that have emerged to foster vaccine R&D capacity and access in lower- and middle-income countries — and which especially characterize the global COVID-19 response — have their origins in earlier efforts to combine complementary expertise and capabilities. Examining these partnerships, both those that worked well and those that did not, offers lessons for future initiatives.

The conjugate meningitis A vaccine showcases a successful partnership. The FDA, a Dutch biotech firm, an Indian vaccine manufacturer and the WHO were all involved in its development, with support from the Bill & Melinda Gates Foundation and PATH, an NGO focused on accelerating health equity. Gavi's role in downstream financing and distribution was also an essential "pull" mechanism that supported vaccine development and production. Intended specifically to prevent recurrent epidemics of meningococcal meningitis in the "meningitis belt" of Africa, a market that was unattractive to other manufacturers, the vaccine was evaluated in countries that later introduced the vaccine. With over 300 million people now vaccinated, the disease has been virtually eliminated in many African nations, preventing tens of thousands of deaths (Sambo et al., 2015).

But partnership-supported endeavors are complex and can also encounter stumbling blocks. The Global HIV Vaccine Enterprise is one example of the need for a reset. The development of an efficacious HIV vaccine faces daunting biological complexities that have not yet been overcome despite more than 30 years of research. Against this background, the enterprise struggled to identify opportunities to significantly influence the overall coordination and strategic direction of the HIV vaccine R&D field and failed to gain meaningful traction. When it became clear that it could not continue as a viable independent organization, it was subsumed into a larger entity, the International AIDS Society, where it primarily focuses on communications and convening efforts for the HIV vaccine field (International AIDS Society, n.d.).

The efforts to accelerate the development of vaccines in response to the 2014-16 Ebola epidemic in West Africa also provide important insights about the value and complexity of public-private partnerships. The absence of shared protocols and the failure of global authorities to communicate how many vaccine doses would be needed, and when, were genuine concerns that needed to be navigated in real time (M. Feinberg, personal communication, July 30, 2020; Wolf et al., 2020). Moreover, the vaccine candidate that ultimately proved to be highly effective in preventing Ebola virus infection (VSV-ZEBOV, now licensed as Ervebo®) had actually been constructed a decade earlier and presumably could have been advanced and ready to deploy much sooner, rather than a year after the epidemic was under way. Unfortunately, the development and investment pathways were not in place at the time of the outbreak, nor were the incentives to attract the necessary partners.

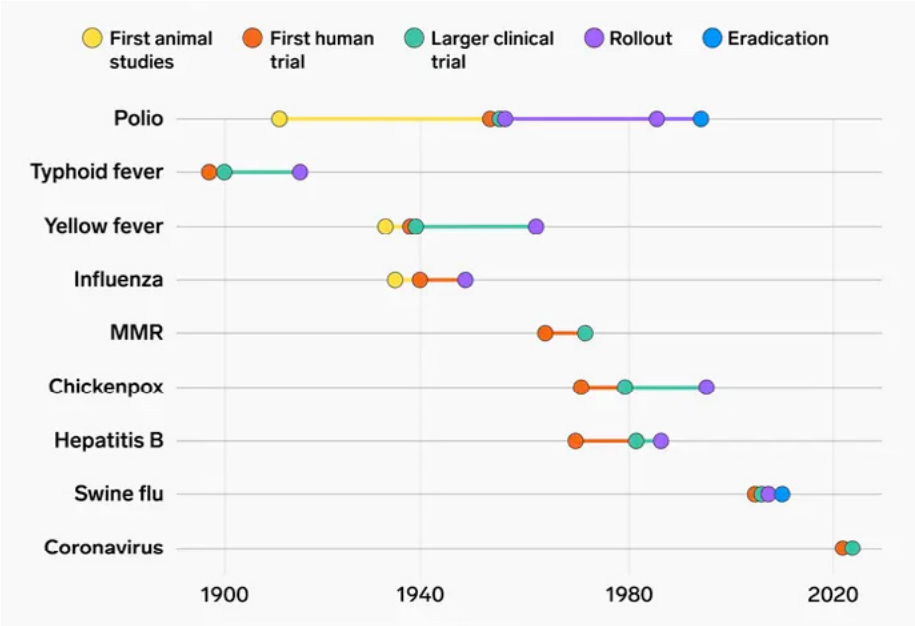
The Ebola epidemic nonetheless offers a number of lessons for vaccine development, including the critical importance of proactive approaches to emerging infectious disease threats and the need for more effective public-private partnership models. The sense of urgency created by the epidemic prompted the FDA to demonstrate more than its routine level of hands-on engagement and regulatory flexibility, just as it did to move COVID-19 vaccines into the market swiftly (Joseph, 2020). By designating the Ebola vaccine as a breakthrough therapy with priority review status, fast-track mechanisms kicked in that

allowed the FDA to provide intensive guidance in the earliest phases of clinical trials, ensuring a speedier evaluation. As part of its review process, the agency coordinated with international regulatory agencies and based its approval in part on research conducted outside the United States (Fritz, 2020). The collective recognition of the importance of acting proactively and aligning multisector stakeholders to address global health security threats was a major driver for efforts to establish CEPI.

THE COVID-19 EXPERIENCE

An in-depth look at the record-breaking response to the COVID-19 pandemic, which resulted in several authorized vaccines within a year, is provided elsewhere in this report (Chagar et al., 2021). Perhaps the most important takeaway is that the R&D enterprise is capable of responding at historic speed in the face of an emergency — but even that speed was insufficient to extinguish the threat. The lessons learned from COVID-19 can now be applied not only in pandemics but also, with suitable adaptations, to vaccines that target endemic diseases, especially where existing vaccines would benefit from improved performance. Figure 2 illustrates the

Figure 2. Comparing Vaccine development throughout history



Source: The College of Physicians of Philadelphia; WHO; CDC; National Institutes of Health; Business Insider.

> Perhaps the most important takeaway is that the R&D enterprise is capable of responding at historic speed in the face of an emergency — but even that speed was insufficient to extinguish the threat.

development timelines for previously approved vaccines; the hope is to institutionalize strategies to shorten these considerably.

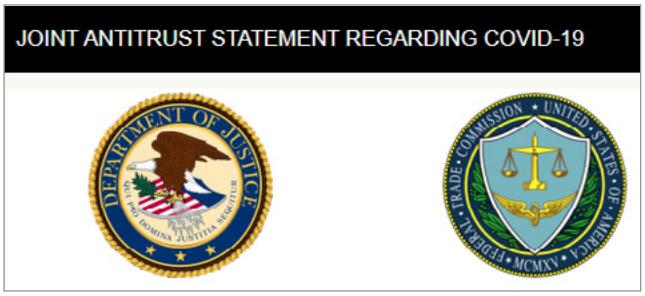
A measure of luck may be part of the COVID-19 success story; the modified spike protein that has been the basis of most major vaccine research thus far appears to be an ideal antigen for priming the immune system. Had the virus featured the immune-system-dodging properties of HIV or some of the other challenges that characterize malaria and TB vaccine development, the outcome could have been very different.

Instead, experience with other coronaviruses (notably, SARS-1 and MERS) enabled researchers to quickly grasp that the spike protein was a promising vaccine target, and cutting-edge technology was ready once the virus was sequenced. Ironically, timing also worked in favor of the COVID-19 vaccine trials. There was so much virus circulating in the United States, the United Kingdom, Brazil and elsewhere that it was possible to compare infection rates in vaccinated and placebo study arms relatively quickly.

However, the appearance of variants capable of evading immunity represents a new challenge that may require other approaches, especially since different vaccines may have varying degrees of efficacy as the virus mutates. Where feasible, trials that allow direct, head-to-head comparisons between vaccines could be of benefit. There has also been a call for broadly protective, "variant-proof" COVID-19 vaccines (Burton & Topol, 2021), which echoes the group's earlier recommendations for a universal influenza vaccine, which reflects the undiminished threat of an influenza pandemic (Sabin-Aspen Vaccine Science & Policy Group, 2019).

Whatever debt is owed to chance, the vaccines could never have been ready for quick study had it not been for prior investments in basic science and global R&D preparedness. Many other factors also helped to facilitate vaccine development — the urgent threat of the pandemic; an unprecedented willingness to share discoveries and partner on research (Isaacson, 2021); government commitments in the form of financial support and direction, including advance market commitments that greatly lessened financial risk; philanthropic funding; national pride; corporate pursuit of reputational benefit; and regulatory flexibility. Partnerships that had previously been used primarily to advance vaccine R&D in lower- and middle-income countries became ubiquitous, bringing together many combinations of

companies, government agencies, academic researchers and NGOs. This was encouraged by the U.S. Department of Justice and the Federal Trade Commission, which issued a joint statement shortly after the pandemic surfaced with guidelines on how usually competitive firms could collaborate without violating antitrust laws (U.S. Department of Justice, 2020), building on the antitrust authority that had been given to BARDA (Pandemic and All Hazards Preparedness Act, 2006).



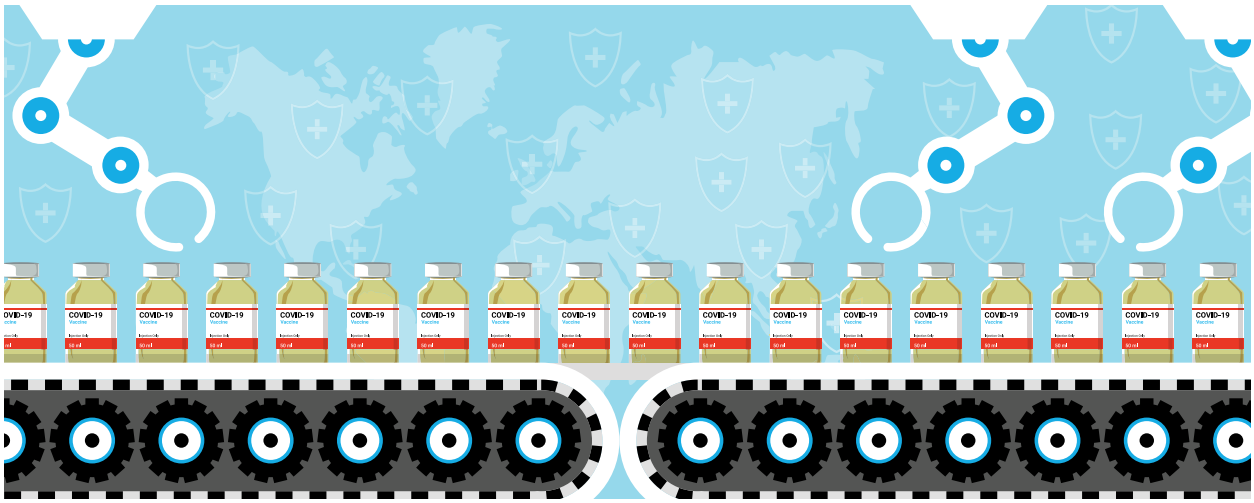
As of September 2020, about half of all COVID-19 vaccine candidates, including most of those in clinical trials, were being developed through partnerships. Almost half paired two research entities, while just over 40 percent coupled a research entity with a development, manufacturing and commercialization player (Chagar et al., 2021). Pairings included a multinational corporation/biotech partnership and a public sector/private sector team, while other agreements linked multinational corporations, corporate and academic teams, and NGOs and biotechs.

These formal partnerships have been supplemented by a remarkable degree of transparency and a willingness to share results in many quarters. COVID-19 also helped to drive new players into the market. Only 14 percent of the organizations involved in development had previously commercialized vaccines, but many others were not entering the race de novo, having already developed their "pandemic response muscles" through prior experience with Zika, Ebola, MERS, SARS-1, H1N1 or global influenza initiatives (Chagar et al., 2021).

The availability of government and philanthropic funding to develop, produce and purchase COVID-19 vaccines — an estimated $13 billion, excluding China's investment (Chagar et al., 2021) — has been fundamental to speed. BARDA grants and advance market commitments alone exceed $10 billion (A Bigger Dose, 2020). Normally, each step in vaccine R&D depends on the success of previous steps, as well as evolving market calculations. But with governments removing much of the financial risk while offering technical assistance and brokering partnerships, industry could simultaneously develop and test COVID-19 vaccines while initiating and ramping up preapproval production through at-risk manufacturing.

The United States has also invoked the Defense Production Act to bolster manufacturing infrastructure and ensure there are no gaps in domestic vaccine production. Particularly

notable were efforts to secure key ingredients and the partnership brokered by the federal government between Johnson & Johnson (J&J), whose vaccine was authorized in late February 2021, and Merck, which agreed to retool its plants to manufacture additional doses of the J&J vaccine. Government authorities agreed to provide the funding and support needed to expedite the availability of equipment, machinery and supplies; coordinate logistics; and repurpose Merck's manufacturing facilities (U.S. Department of Health and Human Services, 2021). Weighed against these benefits, however, is the risk that invoking the Defense Production Act may disrupt the global supply chain, impact vaccine production outside the United States and stymie the flow of vaccines across borders. A similar threat to access surfaces in any country that puts export controls in place.



The various financing mechanisms in use, including research funding, advance market commitments and volume guarantees, are well-described in the background papers published elsewhere in this report (Shulman et al., 2021). While these mechanisms have had a transformative influence on the pace of COVID-19 vaccine development, they also raise vigorous and as yet unresolved questions about whether governments should ask more of the companies they support, particularly by requiring them to share data, assays and other information that is traditionally considered proprietary (R. Bright, personal communication, July 23, 2020).

A clearly articulated and streamlined regulatory process proved critical to the pace at which COVID-19 vaccines were developed, just as it had been for Ebola. In the United States, FDA regulators interacted with developers as clinical trials proceeded. The agency's guidance on efficacy standards, its support for innovative and accelerated clinical trial designs, and the expedited review process all spurred progress. Globally, the WHO's Emergency Use Listing

procedure allowed dozens of countries to authorize the use of COVID-19 vaccines almost immediately after its rapid, rigorous assessment was completed (WHO, 2021a).

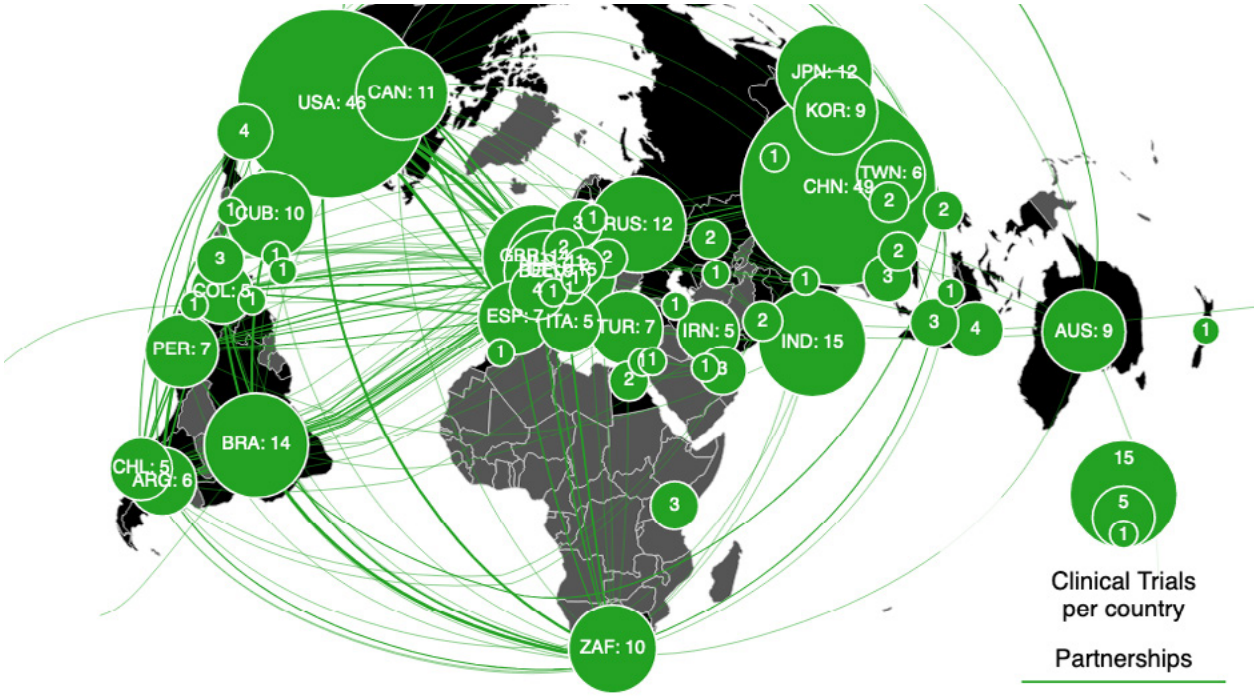
The COVID-19 experience has also highlighted R&D gaps, particularly the lack of global governance and the absence of multinational agreements and funding structures (Lurie & Keusch, 2021; Lurie et al., 2021). In general, many countries pursued their own scientific agendas, with no consensus mechanism for developing research priorities or designing clinical trials with either conventional or novel technologies.

Moreover, no-fault vaccine injury compensation systems have not been established in all countries. A mechanism to compensate individuals who experience a serious vaccine-related injury for routinely recommended vaccines exists in only 25 countries — including the United States, much of Europe and the wealthier parts of Asia, but not in Africa (Mungwira et al., 2020). As these liabilities represent a potentially significant risk to manufacturers, establishing programs and policies to shoulder them provides an important incentive for private sector engagement. Without such protection, manufactures are often reluctant to enter these markets.

While some individual companies reached bilateral immunity agreements with countries that agreed to purchase their COVID-19 vaccines, no entity was initially responsible for ensuring that liability policies and vaccine injury compensation programs were in place prior to vaccine introduction. Recognizing that the COVAX commitment to distribute vaccines in lower-income countries could have been jeopardized without liability protections (Halabi et al., 2020), COVAX created a new program to compensate eligible individuals in 92 lower- and middle-income countries without a need to resort to courts of law. This program, funded by a small levy on each dose, is the first and only vaccine injury compensation mechanism established on a global scale (WHO, 2021b). Going forward, such a system should not have to be reinvented for the next global public health emergency.

Wealthier countries dominate the vaccine R&D sphere, with 70 percent of the research effort led from high-income countries and the remainder from upper-middle-income countries, particularly China and India. South Africa has also played a major role, but a very limited number of clinical trials are taking place elsewhere in Africa, continuing a troubling tradition of excluding the continent from opportunities to gather data on its own population and undermining efforts to strengthen clinical trial capacity (Makoni, 2020; COVID-NMA, n.d.) (Figure 3).

Figure 3. COVID-19 vaccine clinical trials



Source: Romain Vuillemot - LIRIS, École Centrale de Lyon; Philippe Rivière - LIRIS, VisionsCarto; Pierre Ripoll - LIRIS, INSA Lyon; Julien Barnier - Centre Max Weber, CNRS.

Much remains uncertain about future progress against COVID-19. Already by the end of 2020, companies with successful vaccines were facing conflicting pressures to unblind and vaccinate participants in the placebo arms or to maintain them to provide longer-term efficacy and safety data (Cohen, 2020). Subsequent vaccine candidates are likely to be compared to vaccines already on the market, but the 95 percent efficacy rates of the first two U.S.-authorized products set an exceptionally high bar globally. Many vaccine developers are also concerned about the availability of resources since BARDA, CEPI and other funders do not typically support late-stage clinical trials (Chagar et al., 2021). And the emergence of viral variants raises new concerns about the breadth and duration of vaccine protections and the potential need for booster shots or other adaptations.

Unfortunately, though safe and effective, the earliest vaccines authorized in the United States were not ideal for meeting the world's needs because they involve two injections several weeks apart and require complex cold storage, come with relatively high prices and are initially limited by manufacturing capacity. Other vaccine candidates are working their way through the development pipeline, and the U.S.-authorized J&J vaccine, with its simpler storage requirements and single-shot administration, broadens the supply. Nonetheless, there is still concern that first-up vaccines can establish a stranglehold on the market, disadvantaging subsequent vaccine R&D projects that may have other benefits.

These issues are not unique to COVID-19 vaccines, as the broad use of vaccines against pertussis and influenza illustrates. In those examples, their status as the standard of care in a widely vaccinated population makes it challenging for potentially more effective formulations to break through; they are likely to do so only if they can translate into a significant return on investment for vaccine developers.

KEY THEMES

The aggressive and remarkable response to the SARS-CoV-2 virus may well open the door to a new era of vaccines. Expectations could not be higher, given the hope that vaccines will dramatically alter the trajectory of the COVID-19 pandemic and restore a degree of normalcy to life. The convergence of innovations in science and technology with the first-in-a-century worldwide pandemic offers a unique opportunity to establish a new R&D model for pandemics and for the serious infectious diseases that lack vaccines, as well as for innovative vaccines that offer meaningful improvements over those that already exist.

The task ahead is to provide the framework and incentives for standardized approaches to vaccine R&D that encourage continuous streams of innovation while disrupting the cycle of avoidance and neglect that have long characterized the global response to infectious disease. Doing all of that requires strengthened processes, policies and institutions, as well as consistent funding.

In that spirit, these key themes shaped the deliberations of the Sabin-Aspen Vaccine Science & Policy Group:

- **Developing and having timely access to safe and effective vaccines for all people is a moral imperative.** As a foundational component of primary health care systems and a driver of universal health coverage, vaccines impact every sector of society, reaching more people than any other health or social service (Kelleher, 2020). Indeed, they are essential to achieving the 2030 Agenda for Sustainable Development advanced by the United Nations (United Nations, n.d.) and are a core component of the Immunization Agenda 2030, the global vision to ensure that everyone can benefit fully from vaccines, which has been endorsed through the World Health Assembly (WHO, 2020a).

  Yet inequities complicate the R&D component of the vaccine/vaccination ecosystem at every turn. In addition to their immediate impact on the global supply of COVID-19 vaccines, the dominance of wealthier countries in the research, regulatory approval and manufacturing processes fosters inequities in the choice of diseases that become the target of vaccine R&D, the ways in which new vaccines are tested, and access to lifesaving products once they become available.

- **The devastation wrought by COVID-19 demands that we revisit and restructure the vaccine R&D enterprise.** The rapid response of governments, philanthropies, NGOs, companies large and small and the scientific community has shown how the status quo can be modified to move vaccines rapidly through the pipeline. Recognizing the impact of the pandemic on the world's health, social fabric and economic stability, these same players must catalyze the opportunity for transformative change. The effective COVID-19 vaccines that were produced in record time offer a template for revisiting — and perhaps revamping — current approaches. Relatively small infusions of capital from public and private sources enabled development of novel platforms prior to the pandemic, which could then be deployed against the pathogen when it emerged. The roles of dedicated partnerships and goal-oriented funding also suggest strategies for concentrating R&D attention on endemic infectious diseases, albeit on a modified timeline.

- **Scientific breakthroughs and new technology expand ideas of what is possible.** Prior investments in basic science allowed researchers to sequence the SARS-CoV-2 virus, synthesize the spike protein, choose it as the target of a vaccine candidate, prepare it for the mRNA and other platforms and launch human trials within six weeks (Lurie & Keusch, 2021). Those remarkable accomplishments demonstrated the potential of mRNA to create "bespoke protein factories" (Johnson, 2020), one among many examples of how the pandemic's urgency connected seemingly disparate scientific fields. By March 2021,

78 different COVID-19 vaccine trials employing a host of technologies were under way, 22 in Phase 3 (Zimmer et al., 2021).

These approaches remind us of the vital need to continue investing in basic science. They also highlight the value of developing multiple vaccines that take different approaches to the same pathogen, given the difficulty of predicting which vaccine is best suited for a particular disease threat. Although these kinds of efforts may not pay off in the short term — or indeed ever — they nonetheless represent important public health and clinical opportunities, prudent use of financial resources and potential opportunities for profit. As well, they tee up the importance of regulatory science that can keep pace with novel trial designs as they accrue data. COVID-19 is a case study in the ability to streamline regulation without sacrificing quality.

- **A top-down, bottom-up approach, guided by coordinated leadership at all levels, advances vaccine R&D most effectively.** Individuals working across different disciplines, organizations and governments are critically important to the R&D effort, but none operate optimally alone. Vaccine R&D is a team sport, one that requires champions and a mix of innovative, self-motivated groundwork and organized systems within a leadership structure that integrates the knowledge and experience of all contributors.

  The current model of a "conductorless orchestra" has failed to provide the coherent end-to-end strategy essential to efficient vaccine R&D. While space needs to be available for unstructured, out-of-left-field discoveries, conductors of some sort are also needed to guide the many players within a larger framework so that ideas can bubble up, projects can be linked and gaps can be identified to achieve essential goals.

- **Public confidence in the R&D process is imperative to the ultimate goal of reducing the toll of vaccine-preventable diseases.** Trust in the integrity of every component of the vaccine/vaccination ecosystem — assurance that science and public health concerns are paramount drivers of the research, development, approval and distribution process — safeguards the entire enterprise. Confidence elevates support for research, including basic science, and ensures widespread use of safe and effective vaccines once they are available.

The rise in vaccine hesitancy explored in the group's previous report, *Meeting the Challenge of Vaccination Hesitancy* (Sabin-Aspen Vaccine Science & Policy Group, 2020), threatens to undermine progress in vaccine development as well as vaccination. The recommendations in that report, including building a strategic narrative that focuses on the achievements and promise of vaccinations, are designed to generate the confidence essential to widespread adoption of safe and effective vaccines.

FIVE BIG IDEAS TO POWER VACCINE R&D

While the core components of the vaccine/vaccination ecosystem have served us well in many ways, the pressing threats of emerging and long-standing diseases, coupled with novel science and technology, call for further action. Based on its deliberations and the themes that emerged from them, the Sabin-Aspen Vaccine Science & Policy Group offers five big ideas to overhaul R&D and establish a new normal to accelerate the availability of vaccines to combat both pandemic and endemic diseases:

Define leadership roles, responsibilities and mechanisms of accountability to prepare for the R&D demands that surface in a pandemic. The global organizations that now have core roles to play in vaccine R&D should map out a real-time vaccine response so that they are ready to act as infectious diseases emerge or spread. A multipronged structure that anticipates R&D needs before they become acute and delegates responsibility for each part would be the matching bookend to the coordinated efforts represented by COVAX, which was developed to ensure access to vaccines around the world once they are approved. An explicit, well-defined strategy — essentially, a flowchart of who is to do what and when, and who is ultimately accountable for each action — is essential so that vaccine R&D is timely, streamlined, equitable and comprehensive.

The speed at which COVID-19 vaccine R&D moved forward amply demonstrates the power of cooperation and vast resources but also highlights limitations. Mechanisms for sharing newly discovered viral strains and subsequent mutations, intellectual property rights and liability

protection all proved to be "orphan" problems — no one was responsible or accountable for them. Each potential showstopper had to be addressed under the intense pressure of a pandemic. Likewise, strategies for forging partnerships to develop and swiftly test new vaccines in lower- and middle-income countries and opportunities for the efficiencies of regulatory harmonization had not been the focus of advance planning.

The group does not believe a new entity is required to write the rules of engagement so that these and other challenges can be considered in a measured way. Rather, that work should be undertaken by a multistakeholder alliance of institutions already engaged in the vaccine/vaccination ecosystem that come together to reach consensus on a systems approach.

> An explicit, well-defined strategy — essentially, a flowchart of who is to do what and when, and who is ultimately accountable for each action — is essential so that vaccine R&D is timely, streamlined, equitable and comprehensive.

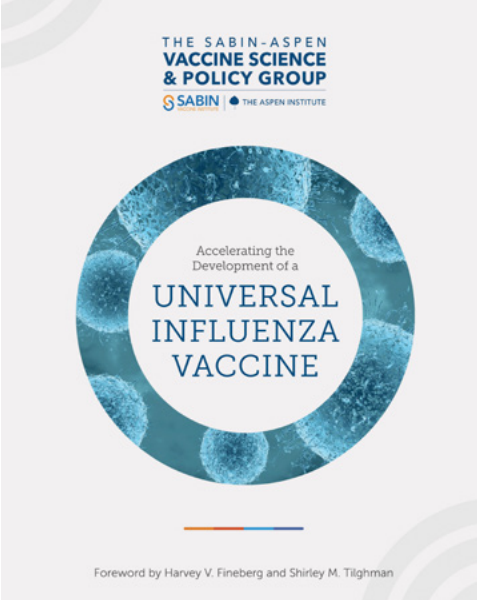
These partners should convene in structured planning sessions to determine the key issues that need to be addressed and to make decisions about who will be responsible for taking them on. Participants also need to devise clear lines of communication, determine how they will intersect with one another as needs evolve and ensure adequate capacity, including funding and human resources. A truly global consensus on how to move forward, framed around the belief that vaccines are a public good, will require a multicentric leadership model that engages partners not only in the United States and Europe but also in China, Brazil, India and the African nations. Attention to aligning incentives for furthering vaccine R&D should be a priority for this convening (see the last big idea, below).

With the key players collaborating, a similar consensus-building process to advance vaccine R&D for endemic diseases should be pursued. Here, too, the goal of negotiating and assigning roles and responsibilities, and establishing accountability, is to streamline the R&D process. A systems approach has the potential to surface opportunities for efficiencies and processes that can shorten timelines and lower costs, making public health investments more viable and commercial pursuit more tempting.

Propel a transdisciplinary research effort built around partnerships to expand and advance vaccine science. Nothing in recent times has showcased the payoff of basic science investment as much as COVID-19 vaccines — a "decades-long overnight success story" that drew on years of earlier research to confront a devastating new virus. The breakthrough in

platform science reflected in the mRNA delivery system was especially noteworthy, but it is not alone. That vaccines are being delivered and beginning to change the trajectory of the pandemic in less than a year is a testament to the power of partnerships to break down institutional and competitive barriers to scientific collaboration.

Such success can only become routine with intentional efforts to engage people across fields and create space for the kind of serendipity that drives novel research and transformational science. A transdisciplinary research effort should combine basic scientific advances in immunology, genomics, microbiology and vaccinology with the latest in computational, engineering and physical sciences, bringing them together in an environment designed to stimulate creative problem-solving and direct science and technology to unanswered questions. The Bill & Melinda Gates Foundation offers a model for what we have in mind: its Global Grand Challenge for Universal Influenza Vaccine Development seeks "completely transformative approaches, rather than incremental research," and calls for "interdisciplinary collaboration and cross-fertilization from outside the traditional influenza research community" (Global Grand Challenges, 2018).



The Vaccine Group's report, *Accelerating the Development of a Universal Influenza Vaccine* (Sabin-Aspen Vaccine Science & Policy Group, 2019), calls for developing and implementing a directed research agenda to drive innovation. The Sabin Institute's Influenzer Initiative grew out of that report with a commitment to a convergent scientific agenda that merges "expertise from life sciences with physical, mathematical, and computational sciences, and with engineering—a blueprint for innovation that both builds on fundamental knowledge and stimulates novel, cross-cutting discoveries" (Influenzer Initiative,

n.d.). The goal is to integrate existing knowledge and shape new frameworks of inquiry to catalyze fresh discoveries, breakthrough developments and their translation into viable vaccines.

To promote convergence science in the broader vaccine R&D enterprise, the group recommends measures to:

- Foster unexpected discoveries across disciplines that have historically been distinct from one another in both knowledge and methods. The Influenzer Initiative has identified the following scientific fields as offering promising opportunities to cross-pollinate and inform vaccine R&D: synthetic biology, bioengineering, systems biology, biophysics, artificial intelligence/machine learning, bioimaging, bioinformatics/computational modeling, chemical engineering and immuno-oncology.
- Bring together funding mechanisms, leadership and oversight to support a research infrastructure that can advance vaccine science and create opportunities for the novel and risky ideas that percolate from the ground up.
- Leverage lessons from new scientific areas to foster innovation, including improved understanding of the chemistry and physics of vaccine formulation, the immunologic basis of protection and correlates of protective outcomes.
- Distinguish between the intensity of the R&D efforts needed in the face of a potential pandemic and those for long-standing endemic diseases. Research in one arena should inform the other, allowing resources to be allocated as efficiently as possible.
- Ensure that an incentive structure exists to promote and support transdisciplinary research (as discussed in the last big idea, below).

Reimagine clinical trials. Clinical trial design is ripe for more efficient and nimbler approaches. The high evidentiary barriers currently required to establish vaccine safety and efficacy have limited innovation and commercial motivation to pursue new products. In particular, the large-scale enrollment and long duration required for Phase 3 trials have been impediments. It is possible to develop better systems without compromising standards — the pace at which researchers assembled a compelling body of evidence for Ebola and COVID-19 vaccines suggests ways to overhaul current practices.

Equity and efficiency must be prime drivers. While vaccines for most endemic diseases enroll large numbers of participants from lower- and middle-income countries — because that is where the diseases most often occur and where vaccines can be evaluated in field settings — enrollment has been much less robust where high-income countries also have significant disease burdens, as is the case with COVID-19. Countries with more limited resources must not only have their populations well represented among study subjects but also must become full partners in clinical trial development from its inception. Developing research capacity and local trial networks, ensuring that the questions under investigation are relevant to local needs, and sharing results with the affected communities are all essential to establishing a sense of shared ownership in the studies.

Because it may be difficult to predict which approach is best suited for a particular disease threat, another important priority is encouraging vaccine trials that take aim at the same pathogen in different ways. The present system often forces promising candidates to drop out after a competitor succeeds, because the barriers to testing subsequent generations of vaccine become too high. Alternative strategies are needed to encourage a more dynamic market, especially after first-generation products become available. These strategies include:

- Establishing global networks of clinical trial sites for vaccines. In the interests of equity, good science and timely results, these sites must fully reflect the diversity of the world's people and be prepared to enroll participants as needs arise. Integrating knowledge as it accumulates around the world and pooling control groups will speed the data-gathering process and increase confidence and trust in trial findings.
- Making the identification of immune correlates of protection a priority. Bringing together all of the large datasets and analyses of clinical and laboratory information on infected and vaccinated individuals is the pathway to this critical goal. Once such correlates are identified, vaccines can be approved on the basis of smaller and faster trials that bridge from surrogate endpoints established from initial efficacy studies. The absence of clear laboratory measures that equate to a degree of immunity poses a recurring barrier to this goal.

- Advancing the use of master protocols in order to accelerate vaccine trials and make the findings more comparable, with careful attention to strategies that do not discourage innovation.
- Considering opportunities for adaptive trial designs that incorporate a "review and adapt" component at the time studies are launched. By planning for interim scrutiny of accumulating data and employing innovative statistical techniques, researchers may be able to measure treatment effects more quickly, abandon futile treatment arms, establish optimal dosage and refine their knowledge about who is most likely to benefit from a treatment (Pallmann et al., 2018).
- Assessing the value and appropriate use of human challenge trials. In such trials, participants are deliberately exposed to a pathogen in a controlled setting to speed knowledge about vaccine efficacy. Considering how best to design such trials, and when and where they can be used to advance science, is essential to developing suitable guidelines for implementing them.
- Structuring clinical trials to inform future programmatic and policy decisions as well as regulatory approval. Trials that evaluate efficacy in subpopulations categorized by age, gender, illness status, race and ethnicity yield important data that can be used to ensure that vaccines are developed with the end user in mind. Trials also need to answer questions relevant to population impact, such as who will benefit most from immunization and the interchangeability of different vaccines against the same disease. And trial designs that use the same methodology and outcome measures will make head-to-head comparisons of efficacy more viable.
- Expanding well-funded postmarketing studies to assure long-term safety and effectiveness and optimal use at a population level, especially where the trials that inform vaccine approval enroll small populations or are based on short-term findings. The tools used to evaluate safety and effectiveness and to collect data should be standardized for lower-, middle- and high-income settings.
- Pairing postmarketing safety surveillance with a commitment to advancing vaccine safety science. Understanding the mechanisms of serious adverse events following immunization and identifying "correlates of safety" before they surface in large, population-based monitoring can generate actionable findings more rapidly.

Restructure regulatory science to reflect advances in vaccine R&D. Transformative vaccine discoveries and technology must be accompanied by equally transformative approaches to regulatory science and process. Extensive regulatory requirements are in place not only to assess clinical trial data but also to assure that effective, safe and consistent products emerge from the manufacturing process, especially as the volume scales up. Without compromising safety and efficacy, regulatory science innovations should be pursued to streamline preclinical evaluation; make vaccine trials faster, nimbler and more cost-effective; and enhance product scale-up, manufacturing and postmarketing surveillance. Steps include:

- Harmonizing global regulatory standards and approaches, including requirements for surrogate endpoints and postmarketing surveillance, with strategies in place to provide the training, technical assistance and resource mobilization that regulators in lower- and middle-income countries may need. As well, emphasize consistent documentation requirements and further strengthen the reliance mechanisms established by the WHO for rapid authorization of COVID-19 vaccines to relieve unnecessary burdens on developers.
- Distinguishing between vaccine approval standards that apply only to emerging pathogens and potential pandemics and those applicable to all vaccines. Antitrust waivers, for example, may be appropriate only in emergency situations.
- Examining current regulatory review processes under the FDA's Emergency Use Authorization, the emergency measures permitted by European Medicines Agency, and the WHO Emergency Use Listing procedure, with an eye toward any necessary improvements.
- Developing training to strengthen and extend the global availability of expertise, especially to build regulatory capacity in lower- and middle-income countries and a broader pool of vaccine safety experts and systems to assess adverse events comprehensively.

Position vaccines as a public good and align incentives so that benefits accrue to all sectors of society. Much like a utility, vaccines are a public good primarily in the hands of the private sector. That perspective suggests opportunities to propel R&D forward, building on the recognition that the public everywhere has an interest in the timely availability of safe and effective vaccines and that the companies expect to be rewarded for producing them. Strategies for incorporating this "public good" framework into R&D decision making should be part of the strategic thinking undertaken at the leadership convening proposed in the first big idea, above.

Because we have failed to treat vaccines as a shared interest, incentives to advance vaccine R&D have often been misaligned. Historically, the priorities of public health have not been in sync with those of vaccine developers, and commercial players have resisted attempts by government to establish research priorities that might not align with their own strategic plans or portfolios. For companies motivated primarily by profit, this is particularly evident in the mismatch between the locations where vaccine-preventable diseases are most prevalent and where customers are most able to pay for vaccines. Other evidence of misalignment goes beyond the private sector — for example, the system of academic advancement often serves to discourage researchers from sharing their findings prior to publication.

When the full health and economic value of vaccines to individuals and society is recognized, different considerations come to the fore. Examining the incentives that are currently in place is the springboard for actions to better align them. While the right strategies need further study, the COVID-19 pandemic offers an opening, having clearly demonstrated the value of inducements that encourage key players to pursue an urgent, singular goal. In those historic circumstances, governments and philanthropies helped to reduce risk, promote partnerships and provide the financial and reputational benefits that inspired commitments.

There are other precedents for this as well, notably the incentives that were developed to entice researchers and companies to study therapies for orphan drugs. Marketing exclusivity, grants and tax credits have all played a role in significantly increasing the number of orphan drugs that have come to market since the Orphan Drug Act was passed in 1983 (Jozst, 2019).

The challenge now is to identify and exploit similar opportunities for other vaccine-preventable diseases in both emergent and nonemergent situations. Agreeing on the research agenda is clearly a front-and-center goal. Manufacturers, researchers and other core partners need to be incentivized to pursue vaccine R&D that takes aim at the infectious diseases posing the greatest risk to regional needs and the broader global community. The nature of those incentives will vary, depending on the respective roles and action drivers of each player and on the urgency of the public health challenge, but reward mechanisms need to be designed by those in a position to offer them — government, philanthropy and academic institutions.

There should also be a strong push to develop or maintain policies and practices that promote information sharing. Several leading vaccine makers released the protocols for their Phase 3 COVID-19 trials, a strategy that should establish precedent rather than being viewed as a special case.

To guide alignment, criteria are needed to help determine which incentives should be offered and under what circumstances and when government requirements may be necessary. The relative urgency of the disease threat is obviously a significant influence. Incentives for manufacturers can include regulatory flexibility, expedited review, guaranteed market share and intellectual property and liability protections. For researchers, opportunities for funding and career advancement may be the most enticing incentives, suggesting that institutional leaders can tie promotion, tenure, awards and other professional accolades to investigations focused on areas of greatest need.

Full consideration to aligning incentives should be part of the proposed leadership convening described above in the first big idea. Importantly, any offer of incentives should demand something back. Public and philanthropic investments in vaccine partnerships and research

initiatives should be conditioned on broadening access to the returns of those investments, such as by sharing data, protocols and findings.

MOVING FORWARD

The big ideas proposed here should be a critical part of any effort to reexamine and restructure the R&D component of the vaccine/vaccination ecosystem. COVID-19 has brought the need for innovation and equity — not only in technology but also in surveillance strategies, partnerships, access to data, genomic sequencing, trial protocols and so much more — sharply to the fore. Experiences with vaccine R&D for numerous other infectious diseases also have much to teach us about what can go right, how to avoid pitfalls and what needs to happen to confront both future pandemics and perennial pathogen threats. Time and preparedness, it is clear, are of the essence to prevent the shattering impact of global pandemics — as well as the chronic devastation of ongoing infectious disease around the globe.

While COVID-19 will offer lessons for some time to come, we have already learned enough to begin to establish new R&D norms. The Sabin-Aspen Vaccine Science & Policy Group looks forward to working with all of those involved with restructuring the vaccine/vaccination ecosystem to move this agenda forward in creating a new normal for vaccine R&D.

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Part 2

BACKGROUND PAPERS

UNDERSTANDING THE VACCINE ECOSYSTEM: STRUCTURE AND CHALLENGES

Stefano Malvolti and Karyn Feiden

INTRODUCTION

Vaccines are recognized as one of the most cost-effective public health interventions available, yet the global vaccine ecosystem is not structured to fully realize their potential to improve health. Systemic constraints are preventing or slowing the development of a large number of scientifically possible candidates.

This paper describes the existing vaccine ecosystem; the influences on the decision making processes of developers; the challenges that arise between a vaccine candidate's transition into Phase 2 clinical development and first country introductions; and their impact on cost, development time and public health benefits. The background and analysis here provide content to inform solutions that can break down systemic barriers limiting the availability of vaccines.

CHARACTERIZING THE VACCINE ECOSYSTEM

To gain insight into ecosystem dynamics, the research that supports this paper identified 61 vaccines that had reached at least Phase 2 clinical development from 2009 to 2019 and then narrowed the analysis to 33 vaccines, primarily for emerging infectious diseases with epidemic potential, diseases relevant to the risk of antimicrobial resistance and neglected diseases (see Table 1). (Each of those vaccines can be considered proxies for other diseases and vaccine candidates with similar characteristics.)

Table 1. Diseases and candidate vaccines included in this analysis[1]

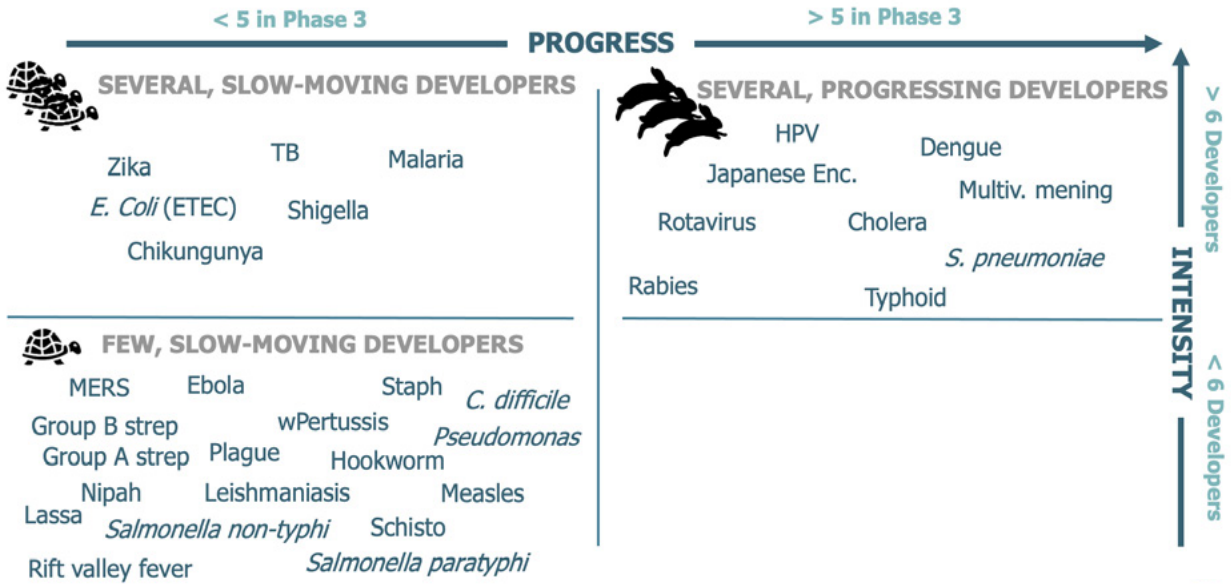
DISEASES	
Chikungunya	Nipah
Cholera	Nontyphoidal *Salmonella*
Clostridium difficile	Plague
Dengue	*Pseudomonas aeruginosa*
Ebola	Rabies
Enterotoxigenic *Escherichia coli* (*E. coli*) (ETEC)	Rift Valley fever
Group A *streptococcus* (Group A strep)	Rotavirus
Group B *streptococcus* (Group B strep)	*Salmonella paratyphi*
Hookworm	*Salmonella typhi* (typhoid)
Human papillomavirus (HPV)	Schistosomiasis
Japanese encephalitis (JE)	Shigella
Lassa fever	*Staphylococcus aureus* (*S. aureus*)
Leishmaniasis	*Streptococcus. pneumoniae* (*S. pneumoniae*)
Malaria	Tuberculosis (TB)
Measles	Whole-cell pertussis
Meningococcal meningitis (monovalent C and multivalent)	Zika
Middle East Respiratory Syndrome (MERS)	

Source: MMGH Consulting for the Wellcome Trust, 2020.

[1]The analysis did not include these diseases/vaccines: anthrax, candidiasis, Crimean-Congo hemorrhagic fever, cytomegalovirus, enterovirus A71, Epstein-Barr virus, *Haemophilus influenzae* type b (Hib), hantaviruses, hepatitis A/B/C, hepatitis E, herpes simplex type 2, human immunodeficiency (HIV), human metapneumovirus (hMPV), Lyme borreliosis, non-typeable *Haemophilus influenzae*, norovirus, pandemic influenza, polio, respiratory syncytial virus (RSV), Ross River virus, seasonal influenza, smallpox, syphilis, tick-borne encephalitis, tularemia, varicella, Venezuelan equine encephalitis, West Nile Virus, Western equine encephalitis, yellow fever or zoster.

Most vaccines that target neglected diseases and diseases related to antimicrobial resistance are characterized by the presence of few developers and a small number of late-stage clinical trials. Exceptions, primarily relating to TB and malaria, cluster in an intermediate space, where several developers are engaged but there is slow progress into late-stage clinical development (see Figure 1). By contrast, second-generation vaccines that enhance an existing product (e.g., vaccines with more serotypes, combination vaccines) are characterized by a higher number of developers and late-stage clinical trials. Vaccines for emerging infectious diseases with epidemic potential enjoyed slightly more attention because of their global reach. In this space, the impact of the Coalition for Epidemic Preparedness Innovations (CEPI) is still too hard to assess since it was only launched in 2017 and its candidate vaccines were not yet sufficiently advanced during the 2009-2019 time frame of this analysis.

Figure 1. Status of development for vaccines included in this analysis



Source: MMGH Consulting for the Wellcome Trust, 2020.

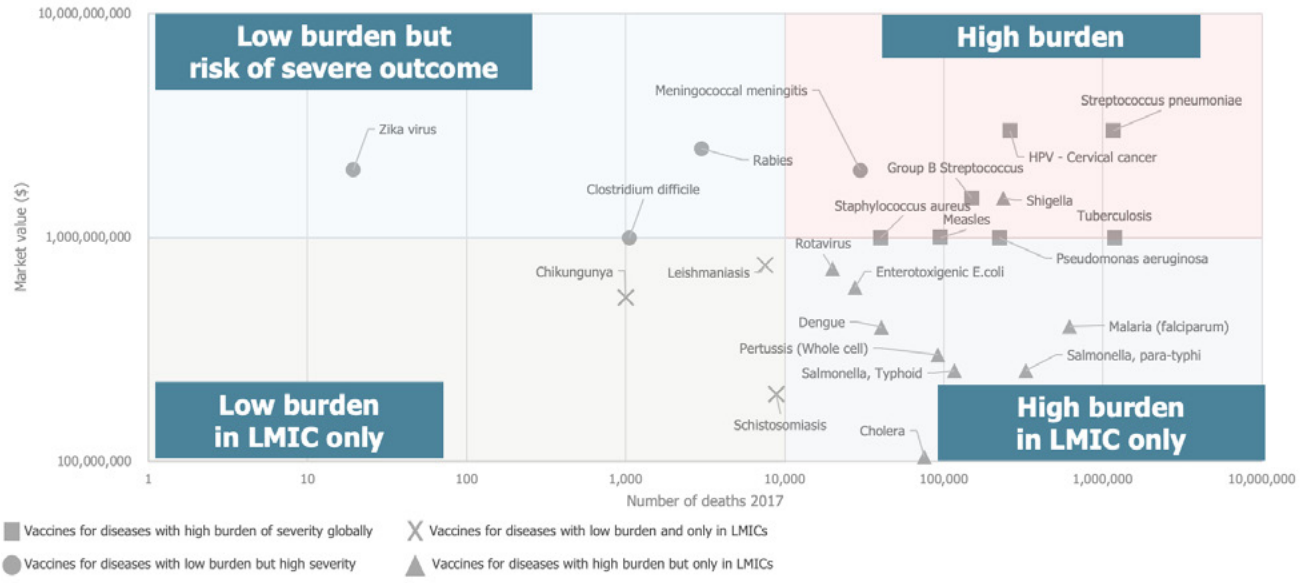
In general, technical and regulatory challenges; marketing and financial realities; and insufficient interest from policymakers, funders and developers limit the existence and pace of many vaccine development programs and discourage innovation. Overall, the level of engagement by vaccine developers is mostly associated with the projected size of the financial opportunity, with more engagement where the global burden or risk of severe

disease is higher, and the risk of development, with more engagement where existing technology and established knowledge reduce the risk.

Twenty-four of the examined diseases and associated vaccines have estimated market values above $100 million per year, and these revealed a weak correlation (r = 0.31) between market value and the number of developers, indicating that developers have a moderate preference for markets with a higher value.

Research also showed a higher market value for vaccines against diseases that carry a high global burden of deaths compared to diseases where the burden, even if large, is concentrated in low- and middle-income country settings. Low-burden diseases that carry the risk of severe outcomes globally tend to have high market value, similar to high-burden diseases (see Figure 2).

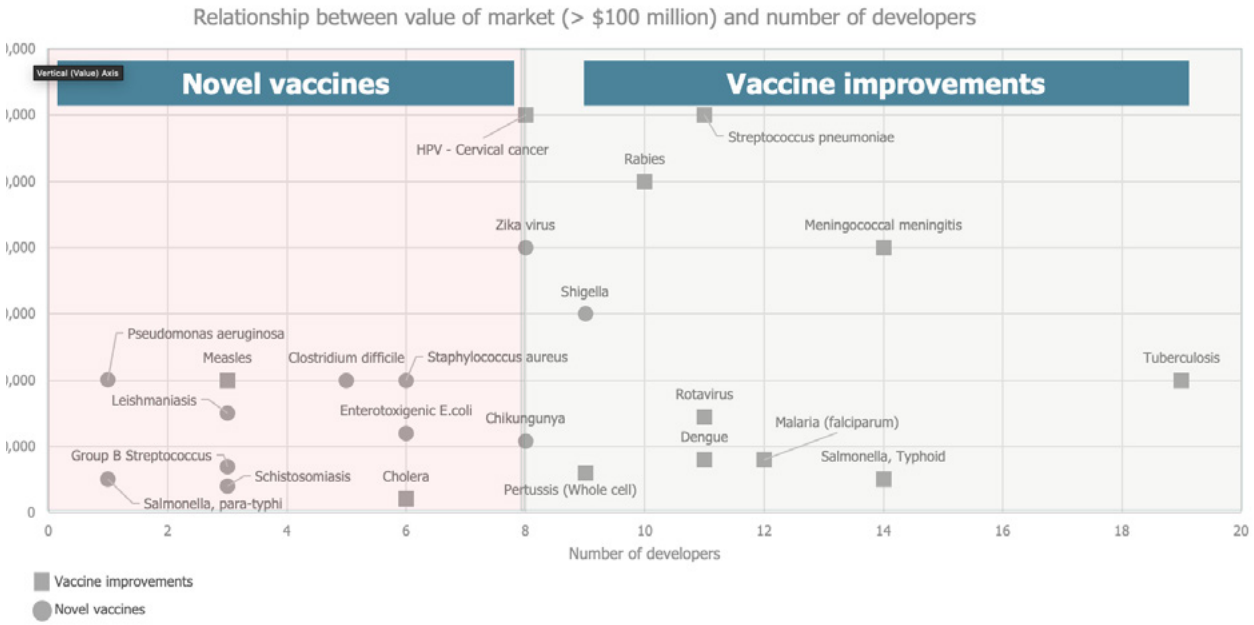
Figure 2. Clustering vaccines by burden of disease and income level



Source: MMGH Consulting for the Wellcome Trust, 2020.

Given that most of the vaccines studied here have relatively low market values, the level of development risk — as defined by their use of technology that has already been proven and approved by a regulator and by the existence of an established market — emerged as a critical influencing factor. Low development risk attracted more developers, regardless of market value (see Figure 3).

Figure 3. Clustering vaccines by degree of development risk



Source: MMGH Consulting for the Wellcome Trust, 2020.

INFLUENCES ON DECISION MAKING

The decisions that vaccine developers make about continuing, delaying or stopping development are influenced by many internal and external events and by factors that change over time and have varying degrees of influence, depending on the type of developer involved (e.g., an academic institution or a multinational company with a portfolio of licensed vaccines).

Internally, clinical trial results are the most likely trigger for a developer to review a decision to proceed on a vaccine. Scheduled reviews, such as comprehensive scientific- or business-focused project and portfolio reviews, are also relevant, particularly for large manufacturers.

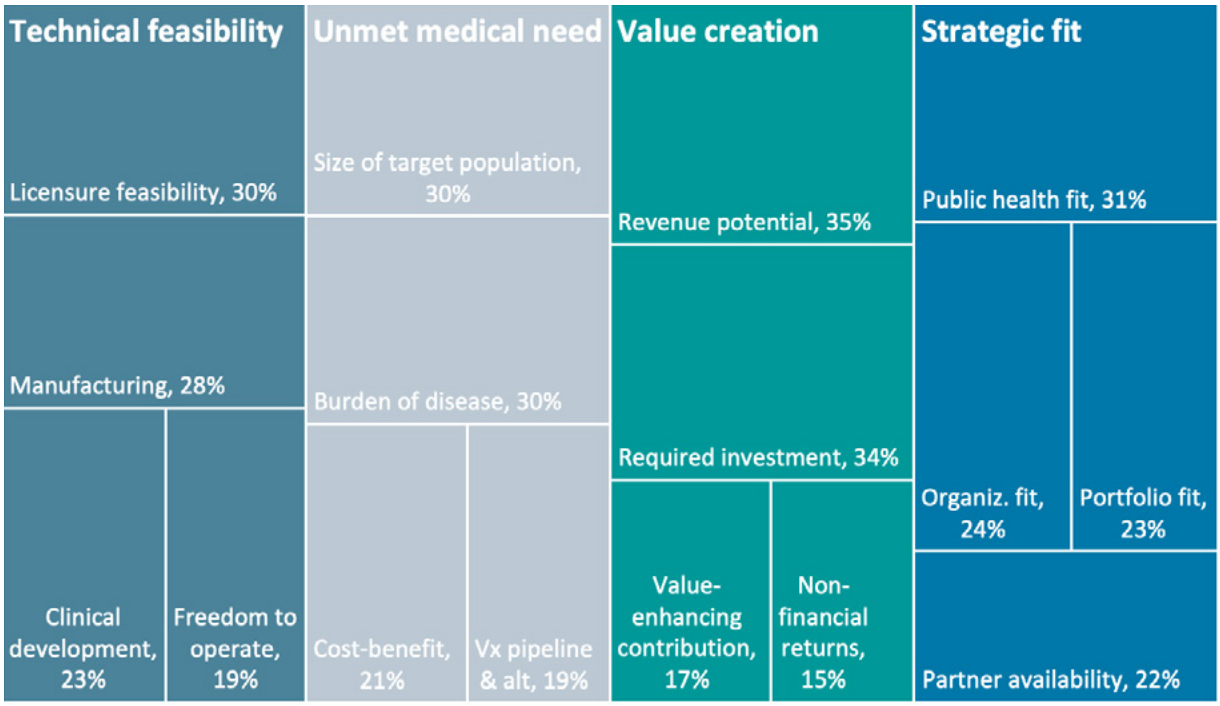
On a more ad hoc basis, corporate events, such as leadership changes or the selection of research, manufacturing and financing partners, can influence decisions. So, too, can business opportunities, such as the acquisition of a product under development, a merger with another developer or a technology transfer. As well, unplanned events during a clinical trial, such as significant recruitment delays, may require immediate intervention and development decisions.

Externally, push events that stem from shifts in the environment or pull events intended to influence vaccine development are also important decision triggers. Disease outbreaks are especially impactful, as are emerging safety concerns, supply shortages and other specific events, especially those that generate pressure from stakeholders or the media. New financing opportunities, mergers and acquisitions, changes in competition or regulatory policy and scientific advances can also push vaccine developers to reconsider their decisions.

Pull factors include the availability of new financial incentives, such as advance market commitments or priority review vouchers, a recommendation for vaccine use by the World Health Organization (WHO) or priority status in the Gavi Vaccine Investment Strategy.

A survey-based analysis of what drives the decision to move to the next phase of vaccine development uncovered four broad areas of influence: (1) technical feasibility, (2) unmet medical need, (3) value creation and (4) strategic fit, with a set of sub-factors under each category (see Figure 4).

Figure 4. Relative importance of sub-factors within broad categories of influence



Source: MMGH Consulting for the Wellcome Trust, 2020.

TECHNICAL FEASIBILITY

The technical feasibility of vaccine development is most influenced by:

- **Licensure feasibility:** The requirements of the reference regulatory authority are the most important, followed by the selection and sequencing of countries where the vaccine will be licensed in its first years.
- **Manufacturing process characteristics:** Almost all manufacturing-related factors have significant influence on progress. Scalability is most critical, followed by quality control requirements. The complexity of the manufacturing, the reflecting technology, the required size of the manufacturing facility and the vaccine design are also germane.
- **Clinical development feasibility:** The probability of success has the most influence on decision making, followed by the emerging safety profile, as assessed from clinical trials. The expected size and difficulty of the pivotal trial(s) — a consequence of the disease epidemiology, the target countries, the design of the clinical trials and the position of the reference regulatory authority — are also key.
- **Freedom to operate:** Access to all required intellectual property, whether through ownership or licensing arrangements, is important, especially in the early phases of vaccine development.

UNMET MEDICAL NEED

The factors related to unmet medical need most likely to influence vaccine development decisions are:

- **Size of the target population:** The size of the target population, as defined by epidemiological parameters, is a measure of the magnitude of the problem and a key reference point for vaccine development decisions.
- **Burden of disease:** Mortality and morbidity emerge as the most relevant influences here. Periodicity and frequency of a disease are also relevant, while disability-adjusted life years and probability of outbreak occurrence are least important.
- **Cost-benefit equation:** The perceived importance of the disease to policy makers — not the actual calculation of a cost-benefit ratio — is the most important factor because policy makers generally make decisions based on input that goes beyond a quantitative assessment. Strong evidence of cost-effectiveness is also an important influence.

- **Vaccine pipeline and alternative treatments:** The existence of a rich pipeline for vaccines, a proxy for the degree to which medical need is truly unmet and a measure of the perceived level of direct competition, is key. The availability of other preventive and therapeutic interventions is also relevant, although to a lesser degree.

VALUE CREATION POTENTIAL

Elements of value creation that influence vaccine development decisions include:

- **Revenue potential:** Through the lens of revenue potential, time to licensure emerges as the most influential factor in moving forward with vaccine development, followed closely by the likelihood that a vaccine will be recommended for global use and by the willingness and ability for costs to be covered at the country level.
- **Required investment:** The magnitude of the investments required for clinical development and manufacturing setup are the most influential decision making factors.
- **Value-enhancing contribution:** The availability of internal funds is a key influence, as is access to grant funding, which reduces the financial obligation on developers.
- **Nonfinancial returns:** Societal and reputational impact both have significant influence on decision making, depending on the position and strategy of a particular company.

STRATEGIC FIT

Strategic fit, both within the developer organization and the broader public health context, influences decisions:

- **Public health fit:** Strong support from key global health stakeholders and a clear WHO position have substantial impact. The presence of strong, disease-specific opinion leaders and advocates to support clinical trials and influence policy decisions is also important.
- **Organizational fit:** A strong internal champion and the alignment of a vaccine with the priorities of important stakeholder groups on the developer's board are also important influences.
- **Portfolio fit:** The availability of a vaccine "platform" — in which more than one vaccine uses similar technical approaches or targets similar customers synergistically — can influence vaccine development decisions.

- **Partner availability:** The availability of a partner interested in sharing the financial burden of development plays a key role, especially among companies that have no licensed vaccines. The latter group also ranks the importance of technology and manufacturing partners higher than those that already have vaccines on the market.

INFLUENCES ON DECISION MAKING BY PHASE OF DEVELOPMENT

While the focus of this analysis is on the factors that influence vaccine development after Phase 2, many decisions are made much earlier, especially when there is an overriding public health need or motivation to advance development quickly. SARS-CoV-2, of course, is the paramount example at the moment. In such circumstances, decisions can be compressed to take place in parallel, diverging significantly from the typical process.

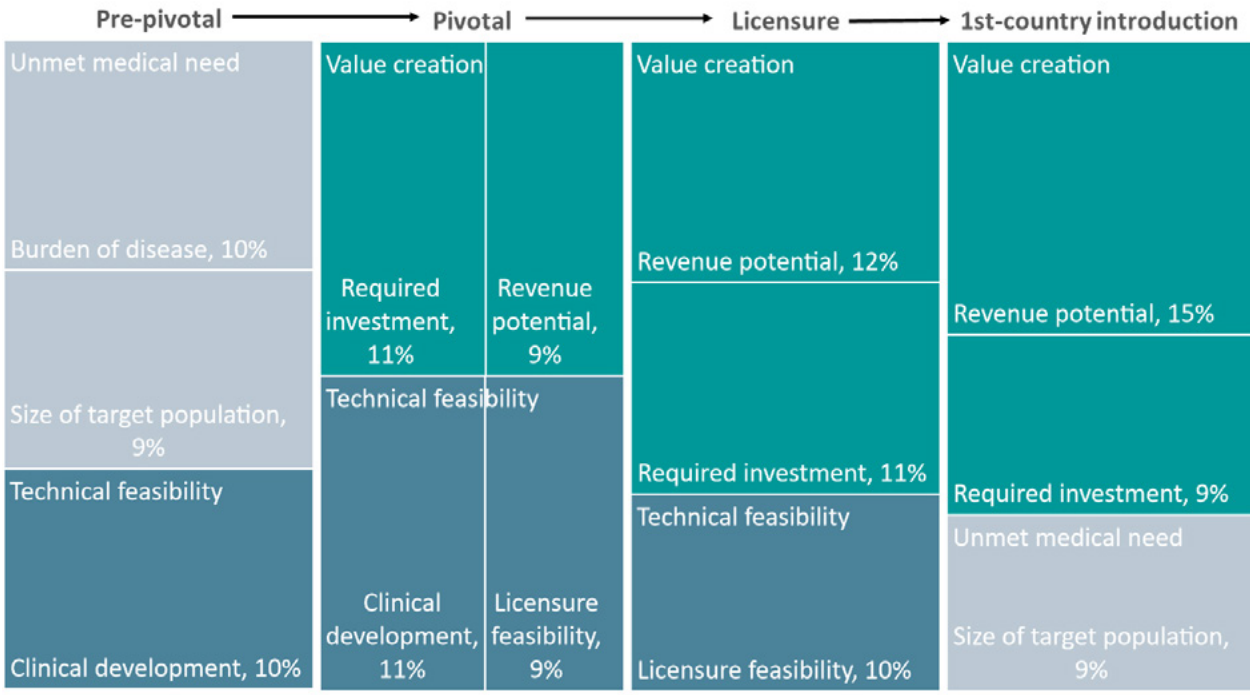
The result is that the relative importance of the factors that influence decision making is likely to shift. Although certain external and technical factors (such as establishing a minimum safety profile) must still progress in a structured pattern, others, such as the potential to create value, may be considered somewhat differently. In this evolving environment, the standard sequence of vaccine development is less strictly delineated. Figure 5 presents the relative importance of decision making influences in the context of an evolving vaccine life cycle that moves more swiftly from early research through commercialization.

In the *pre-pivotal* phase, which includes the decisions made through Phase 2, unmet medical need and technical feasibility are the most important factors. Technical feasibility continues to be an influential factor in the subsequent *pivotal trial* phase, covering the decisions beginning with the transition into Phase 3 and continuing through that phase. Within the category of technical feasibility, the feasibility of clinical development and licensure emerge as the most significant sub-factors.

As development programs progress toward commercial development, creating value assumes the greatest influence on the decisions of vaccine developers. The revenue potential and total required investment are key factors as *licensure* is pursued. In the *first country*

introduction of a licensed vaccine, the dominant influence is value creation, which is typically a function of the target population that has been identified and the policy recommendations that have been made, or are under discussion, at the global, regional and country levels.

Figure 5. Leading decision making influences within each phase of development



Note: These are the most important influences, but there are many others, explaining why the percentages do not add up to 100%.

Source: MMGH Consulting for the Wellcome Trust, 2020.

INFLUENCES ON DECISION MAKING BY TYPES OF DEVELOPER

Decisions about which vaccines to pursue, and the range of possible outcomes, are also significantly influenced by the type of organization involved:

- **Large, established manufacturers** are driven by technical feasibility concerns and can readily stop development of an individual vaccine because they are less dependent on a single product. Because large organizations may have alternative ways to generate a larger or faster return on investment, strategic fit and opportunity cost are major influences. Value creation, driven by the need to contribute to overall financial performance, also plays a leading role in decision making.

- **Midsize private companies** with fewer resources are especially concerned about technical feasibility and will likely give special consideration to the portfolio fit of new vaccines. Value potential is essential given their need to focus on vaccines with a favorable business outlook.
- **Midsize national developers** that are either owned by the government or closely aligned with one typically focus only on vaccines of national and regional relevance, emphasizing unmet medical need. The strategic fit with national needs is often the overriding decision making factor.
- **Midsize and small biotech organizations**, which typically have no licensed vaccines, are often willing to take greater risks in terms of technical feasibility and may tenaciously pursue development, adjusting their plans rather than stopping altogether. The potential to create value, whether through continued development or exiting via licensing or acquisition, is a driving force, and unlike large vaccine developers, these smaller organizations may pursue value prior to licensure.
- **Academic and government-associated developers** are influenced by unmet medical need and research that has a strategic fit with their agendas and priorities. These developers are often entirely dependent on external funding to progress to the point at which they can sell vaccine rights, and their decisions may depend exclusively on continued funding.
- **Product development partnerships** tend to focus on specific disease targets or a well-defined mission, much like academic and government developers, but their smaller portfolios make them highly influenced by unmet medical need and strategic fit. The degree to which partnerships have the independence to make decisions with financial implications is dictated by the relationship of each partnership with its funders — some funders may view their influence as primarily technical, while others might incorporate cost-benefit factors.

PRIORITY CHALLENGES

A multitude of challenges cause developers to stop progressing vaccine candidates from Phase 2 clinical testing through licensure and to first country introductions. A literature review and subsequent analysis identified 54 such challenges, which can extend the duration of development, elevate the risk that a developer will not pursue licensing and increase the price of vaccines if they do become available.

Typically, many of the fundamental scientific and technical questions have been addressed by the time of the Phase 2 transition, and the focus of activity has turned toward market economics and the relative uncertainty of demand. From the standpoint of the vaccine developer, decisions to proceed are particularly influenced by the estimated time and cost necessary to proceed and by the strategic fit of vaccine candidates within its portfolio. Based on these factors, the list of priority challenges was narrowed to 16, sorted into four broad categories — (1) regulatory, (2) manufacturing, (3) market and policy and (4) financial outcome (see Figure 6).

Figure 6. Sixteen priority challenges

Source: MMGH Consulting for the Wellcome Trust, 2020.

REGULATORY CHALLENGES

With the transition into Phase 2 clinical development, the focus of regulatory activities turns toward proving the efficacy and safety of a vaccine. In general, an absence of clear regulatory standards and established pathways to licensure, coupled with the limited expertise of most national regulatory authorities (NRAs) and the absence of a global cooperative regulatory strategy, are significant impediments. Among the challenges:

- **Lack of recognized surrogates or correlates of efficacy:** The ability to assess the efficacy of a vaccine by measuring a particular immune response, rather than clinical outcomes, greatly facilitates vaccine development, licensure and subsequent effectiveness monitoring. Absent recognized surrogates or correlates of efficacy, trials must be powered to show protection against disease, which means larger and more costly trials and higher per-dose prices.
- **Lack of support from regulators for alternative clinical pathways:** Studies of human infection are useful for proof of concept, pathogenesis, down-selection, immunogenicity and efficacy studies. Likewise, adaptive clinical trial design with a single control group, step-wedge design and other features can speed up development and allow multiple vaccines to be assessed in parallel (as seen with Ebola and SARS-CoV-2 trials). However, many regulators are reluctant to accept these nonconventional clinical pathways as pivotal trials, preferring that vaccines demonstrate effectiveness against naturally acquired disease in a traditional fashion. This extends the lead time before vaccines become available and generates higher prices once they are.
- **Too few national regulatory authorities capable of regulating the primary licensure of a novel vaccine efficiently and flexibly:** Regulatory capability for novel vaccines is highly concentrated among a small group of government regulators. Although the WHO has sought to expand regulatory capability, evaluate the performance of regulatory authorities and — where possible — confer WHO Listed Authority (WLA) status, there is still a paucity of knowledgeable regulators capable of developing the sophisticated approach needed to guide developers. The relative dearth of authorities able to license innovative vaccines efficiently means that developers must choose between a sophisticated NRA in a country with lesser needs, thus delaying access elsewhere, or an NRA that lacks strong competencies, slowing the licensing process.
- **Lack of harmonized requirements for quality, efficacy, labelling, packaging and the safety of biologicals and diagnostics across NRAs:** Primary licensure of a vaccine with global demand is just the starting point — pursuing licensing in nearly 200 countries adds costs and delays to vaccine availability. The lack of international or regional standards forces developers to meet specific local requirements and possibly to conduct bespoke clinical trials, regardless of clinical or epidemiological needs. The need to establish different safety monitoring processes or meet unique labelling and packaging requirements, for example, adds costs and delays and can reduce access if developers decide not to license their products in certain jurisdictions.

MANUFACTURING CHALLENGES

Efficient commercial-scale vaccine manufacturing is hampered both by a lack of experience in vaccine manufacturing and by the need to make early decisions about the manufacturing process and capacity in order to reduce input costs and generate a reasonable return on investment. Among the challenges:

- **Lack of ability to share production processes or facilities for multiple vaccines:** Because vaccines use many different production technologies (e.g., fermentation in yeast, growth in cell culture or eggs, lyophilization), facilities typically require unique equipment. Even when manufacturers of different vaccines can share equipment or space, an extensive changeover cleaning procedure is required for quality control, often rendering any benefits of a shared facility moot. The fewer the opportunities to share production processes, the greater the time and costs developers incur to establish unique manufacturing lines or facilities. This also raises the risk profile of those investments, reducing the likelihood of "go" decisions.

- **Long lead time to establish and size manufacturing capacity:** Decisions to build a dedicated manufacturing facility or production suite at scale and determination of the appropriate size needed to satisfy projected demand are typically made prior to Phase 3 clinical development. Building and validating a plant can take up to five years to complete and have little to no utility if the final clinical phase is not successful or if the demand is much smaller than expected. Yet waiting to invest in a manufacturing plant until some clinical success is demonstrated or until there is more clarity about demand increases development time because at least some Phase 3 clinical trial material must come from the manufacturing plant where the licensed vaccine will be produced.

- **Lack of partners to receive technology transfer:** Developers unable or unwilling to establish manufacturing capacity themselves face the difficult task of finding partners for both clinical and commercial material. Although many organizations are involved

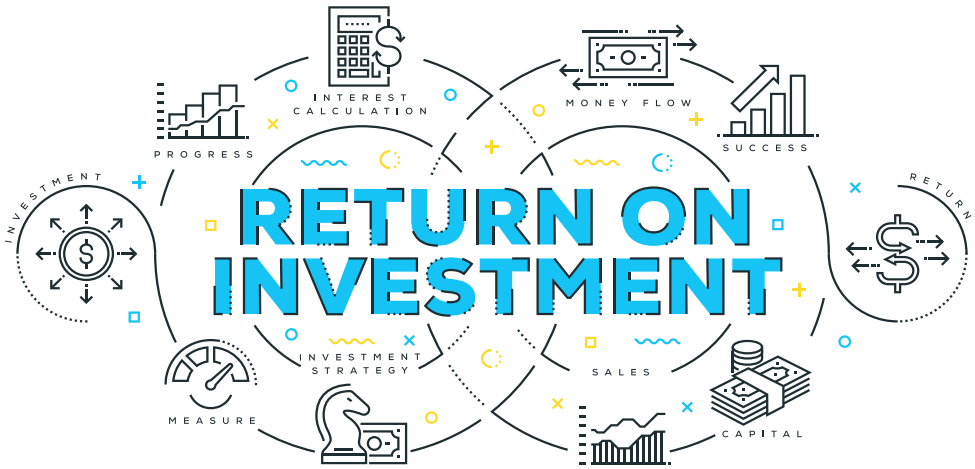
in early- to mid-stage vaccine development, far fewer are capable of manufacturing a licensed vaccine, especially one using more innovative technologies. The inability of smaller developers to identify potential partners can lead promising vaccine candidates to be abandoned.

MARKET AND POLICY CHALLENGES

Market predictability and policy support are strongly related to the feasibility of recouping costs. But vaccine developers operate in a highly uncertain environment because demand is not usually characterized by incremental change but rather by large-step changes that result either from environmental factors (in the case of an outbreak) or national policy (in the case of a new vaccination program). Among the challenges:

- **Insufficient public budgets to purchase and implement immunization programs:** The general state of a country's public finances, pressure on health budgets and political considerations can all constrain governments' ability or willingness to invest in immunization programs. Despite other influences — such as WHO vaccine recommendations, initiatives such as the Sabin Vaccine Institute Sustainable Immunization Financing Program (to assist in public budgeting) and advocacy efforts by developers and other stakeholders — country-level decisions ultimately dictate the scope of vaccination programs. The gap in the use of data-informed and evidence-based advocacy to sustain or increase budget allocations for vaccination programs poses considerable risk to vaccine developers.
- **Lack of data to assess the potential impact of vaccination in target populations and uncertain policy recommendations:** In the absence of rigorous surveillance capabilities and sound epidemiological data, developers are challenged to demonstrate the true impact of vaccination. An uncertain policy environment — especially for vaccines that lack a clearly defined target population, initially target low-income countries, need new implementation strategies or may be affected by the performance of immunization programs — is a further challenge that translates directly into market uncertainty.
- **Lack of appropriate models for economic valuation globally or in certain countries:** Without a solid evidence base that demonstrates the burden of disease and the potential impact of vaccination, or a commonly accepted method for valuing the economic benefits of immunization, it is difficult to advocate for greater public spending on vaccination programs. Relying on cost-effectiveness assessments, rather than considering

broader societal benefits, undervalues the contributions that vaccines can make to better societal outcomes. That, in turn, influences the decisions of policy makers and reduces the appeal of vaccines as research targets.



FINANCIAL OUTCOME CHALLENGES

Generally high development costs and lower revenues for vaccines, coupled with the unpredictable market and funding streams that are ill-suited to the long development timelines and investment requirements of vaccines, all limit the number of developers to secure the necessary capital to proceed to first-country introduction. Among the challenges:

- **Opportunity costs that outweigh the vaccine's economic rationale:** Resource allocation decisions dictate that limited resources be spent on projects with an acceptable return on investment, and generally on those with the highest return. Because of the need for large clinical trials, significant single-purpose manufacturing plant investments and a higher risk profile, vaccines are generally more expensive to develop than other therapeutic categories. Combined with the high degree of uncertainty about revenues, they are also less profitable than other classes of medical products (such as pharmaceuticals for oncology or chronic conditions).
- **Pricing pressure that discourages innovation to improve existing vaccines:** Buyers are often unwilling to pay a premium for presentation improvements, including for features

that result in net savings (e.g., a per-dose price that is higher for a single dose than for a three-dose schedule). This limits developer interest in making improvements and reduces the number of developers and level of competition.

- **Limited availability of aligned partners to commercialize vaccines:** Vaccine developers that lack capacity or interest in pursuing licensure, typically public and academic institutions and smaller developers, must find available partners that can assume ownership of a vaccine, license it and directly or indirectly commercialize it. Globally, fewer than 100 companies commercialize vaccines, and many of them are small entities focused on their domestic markets that are not prepared to act as partners.
- **Insufficient access to funds for late-stage development:** Phase 3 is the most expensive part of vaccine development because of the high risk and long lag before the developer can recoup any return on investment. Very few small and midsize developers can fully self-fund this stage, which can cost anywhere from $30 million to $500 million, depending on the vaccine, the trial and the NRA requirements.

  Identifying and securing funding from the financial markets, as equity or debt, is challenging because investors typically pursue more immediate returns and lenders seek less risky ventures. This is especially true for companies in emerging markets, such as India, where financial markets are less sophisticated and less interested in risky enterprises.
- **Need for expensive manufacturing investments prior to clinical success or demand certainty:** Because it can take as long as five years to complete a manufacturing facility, construction begins well before Phase 3 data are available or licensing has been achieved. Yet the overall probability that a vaccine candidate will fail in Phase 2 is 42 percent (Wong et al., 2019), meaning that production capacity decisions must be made when the risks are quite high. Few large developers can invest "at risk," and others must seek outside support that is likely to be limited in size or to certain diseases.
- **Available incentives (e.g., pull mechanisms) that are not sufficiently attractive for the developer:** Lack of adequate funding and other incentives from governments and foundations deters the development of vaccines that are technically possible, leading developers to concentrate on markets that command higher prices. Private capital is often insufficient to fill the gap, particularly in countries where the financing market is not fully developed.

CONCLUSION

Some of the 16 priority challenges are universal; others have the most powerful influence on one or more of a specific category of vaccines. But all of them add either significant costs to the development process or generate significant delays, and often they do both (see Table 2).

Solving vaccine ecosystem challenges thus presents substantial opportunity for benefits in cost, time and public health (see Table 3).

Table 2. Cost and time impact of priority challenges by decision making phase

Priority challenge	Median cost ($ millions)	Median time (years)	Decision-making phase			
			Pre-pivotal	Pivotal	Registration	1st country introduction
Lack of recognized surrogates or correlates of efficacy	255	5.5	Technical feasibility	Value creation		
Lack of support from regulators for alternative clinical pathways	155	2	Technical feasibility	Value creation		
Too few NRAs capable of regulating the primary licensure of a novel vaccine efficiently and flexibly	55	3	Technical feasibility	Value creation		
Lack of harmonized requirements for quality, efficacy, labelling, packaging and safety of biologicals and diagnostics across NRAs	50.5	3			Value creation	
Lack of ability to share production process or facilities for multiple vaccines	275	3	Technical feasibility	Value creation		
Long lead time to establish manufacturing capacity	275	3	Technical feasibility	Value creation		
Lack of partners to receive technology transfer	50.5	3		Value creation		
Insufficient public budgets to purchase and implement immunization programs	25.5	6.5	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted
Lack of data to assess the potential impact of vaccination in target populations and uncertain policy recommendations	55	6.5	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted
Lack of use of appropriate models for economic valuation globally or in certain countries	25.5	2	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted		
Opportunity costs that outweigh vaccine's economic rationale	300	0	"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted		
Pricing pressure that discourages innovation to improve existing vaccines	251	0	"Unmet need" and "strategic fit" are not impacted			
Limited availability of aligned partners to commercialize vaccine	0	3			"Unmet need" and "strategic fit" are not impacted	"Unmet need" and "strategic fit" are not impacted
Insufficient access to funds for late-stage development	0	5.5	"Unmet need" and "strategic fit" are not impacted			
Need for expensive manufacturing investments prior to clinical success or demand certainty	255	0	"Unmet need" and "strategic fit" are not impacted			
Available incentives (e.g., pull mechanisms) that are not sufficiently attractive for the developer	255	0	"Unmet need" and "strategic fit" are not impacted			

Technical feasibility | Value creation | "Unmet need" and "strategic fit" are not impacted

Source: MMGH Consulting for the Wellcome Trust, 2020.

Table 3. Cost, time and public health benefits of resolving challenges[2]

Challenge	Cost	Time	Public health
▪ Lack of recognized surrogates or correlates of efficacy	●	●	◑
▪ Lack of support from regulators for alternative clinical pathways	●	○	◑
▪ Too few NRAs capable of regulating the primary licensure of a novel vaccine efficiently and flexibly	◑	◑	●
▪ Lack of harmonized requirements for quality, efficacy, labelling, packaging and safety of biologicals and diagnostics across NRAs	●	◑	●
▪ Lack of ability to share production process or facilities for multiple vaccines	●	◑	●
▪ Long lead time to establish manufacturing capacity	●	◑	●
▪ Lack of partners to receive technology transfer	◑	◑	●
▪ Insufficient public budgets to purchase and implement immunization programs	○	●	●
▪ Lack of data to assess the potential impact of vaccination in target populations and uncertain policy requirements	◑	●	○
▪ Lack of use of appropriate models for economic valuation globally or in certain countries	○	○	●
▪ Opportunity costs that outweigh vaccine's economic rationale	●	○	◑
▪ Pricing pressure that discourages innovation to improve existing vaccines	●	○	●
▪ Limited availability of aligned partners to commercialize vaccine	○	◑	●
▪ Insufficient access to funds for late-stage development	○	●	●
▪ Need for expensive manufacturing investments prior to clinical success or demand certainty	●	○	●
▪ Available incentives (e.g., pull mechanisms) that are not sufficiently attractive for the developer	●	○	●

The **full circle** ● represents the greatest benefit to be achieved (in terms of cost, time requirement or public health impact) by solving each challenge, relative to a **half circle** ◑ or an **empty circle** ○, which offer progressively less benefit.

Source: MMGH Consulting for the Wellcome Trust, 2020.

[2] For each disease relevant to each challenge, the public health impact was measured by adding the level of six indicators: global mortality, prioritization by major global health agencies, relevance for impoverished populations, contribution to antimicrobial resistance, level of investment from global donors and the degree to which a disease is top of mind in the general public and for key political decision makers.

Current efforts to address impediments to vaccine development have generally been led by individual institutions, with little global coordination, too often resulting in discordant or duplicative efforts. A more successful approach would tackle the systemic constraints that prevent or delay the development of scientifically feasible vaccines beyond Phase 2 clinical development. An efficient, synergistic and equitable vaccine ecosystem can emerge by considering root causes, looking beyond products for individual diseases, transcending organizational boundaries and interests and questioning established norms.

The SARS-CoV-2 pandemic has instilled a sense of urgency in the pursuit of vaccines. Perhaps that can be leveraged to address the longstanding challenges that have hampered the vaccine ecosystem for decades.

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DESIGNING AN R&D PREPAREDNESS AND RESPONSE ECOSYSTEM FOR POTENTIALLY PANDEMIC PATHOGENS

Nicole Lurie and Gerald T. Keusch

It is mid-September 2020, and SARS-CoV-2 is thriving, continuing to spread wherever well-proven public health measures are poorly implemented. The United States is experiencing deaths equivalent to those that would have been caused by two World Trade Center attacks per week, and on September 11, 2020, the Institute for Health Metrics and Evaluation at the University of Washington predicted that the death count in the United States alone could exceed 415,000 by the end of the year (Institute for Health Metrics and Evaluation, 2020).

It is increasingly clear that full control over the pandemic will remain elusive without a safe and effective vaccine and the willingness of people to be immunized. While vaccines are being developed at unprecedented speed, the goal of "sequence to proof of concept" in four months is not sufficiently ambitious to stop a pandemic in its tracks. Moreover, economic and political realities that are being characterized as "vaccine nationalism" may delay access to a COVID-19 vaccine for half the world's population.

This paper highlights issues for the Sabin-Aspen Vaccine Science & Policy Group to consider as members ponder ways to do better the next time. Undoubtedly, much of the solution will need to emanate from the political will and economic commitment of world leaders. But some can also come from the continued evolution of the research and development (R&D) ecosystem toward what we now characterize as an end-to-end R&D Preparedness and Response Ecosystem. Our views here build from a report we recently prepared at the request of the Global Preparedness Monitoring Board, based on a literature search, background interviews with 54 global leaders conducted during February through Apr 2020 as well as our prior experience in global health issues (Keusch & Lurie, 2020). They lead to three basic

concepts:

- A good pandemic vaccine response must build on a strong, well-functioning, day-to-day system
- One can always start the work, but we can't make up for lost time
- A vaccine response cannot depend on passing a tin cup in the middle of a pandemic

An evolved, end-to-end R&D Preparedness and Response Ecosystem must become the strong, well-functioning, day-to-day system. The challenge is how to get there as fast as possible.

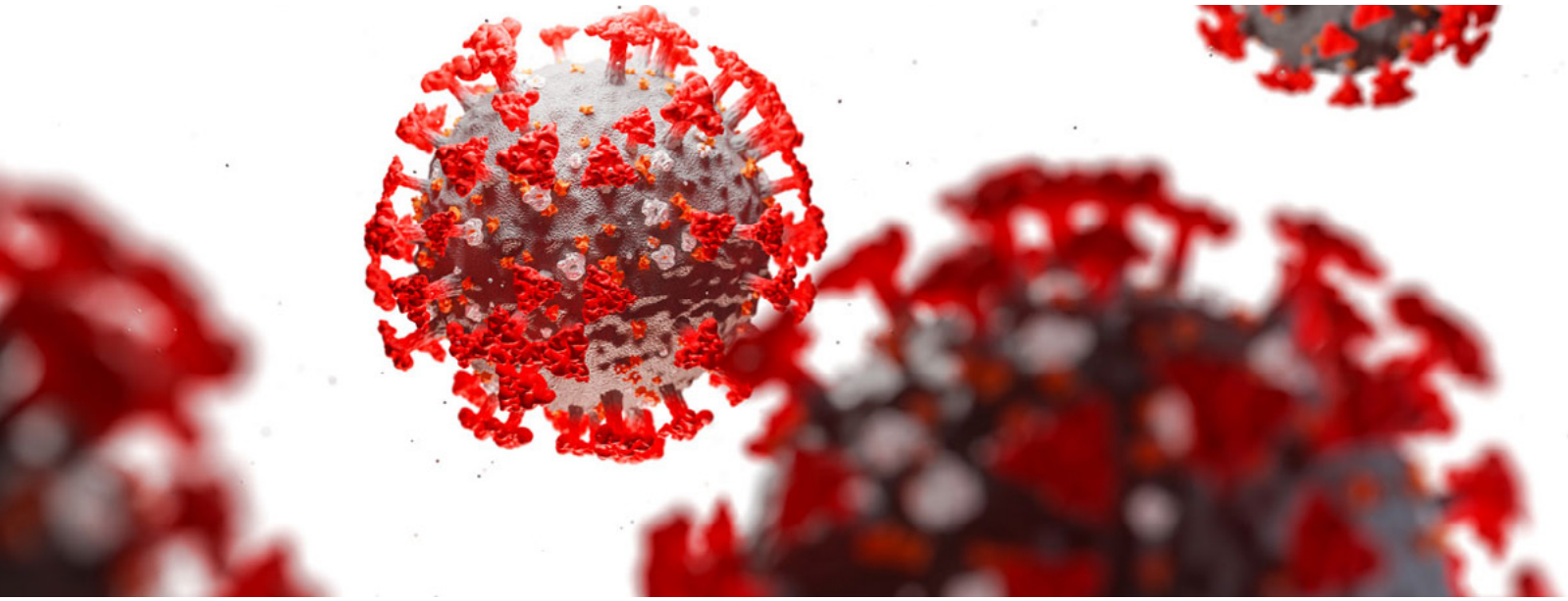
CONCEPTUALIZING AN ECOSYSTEM FOR R&D

The concept of a health sector R&D ecosystem was initially driven by the pharmaceutical industry's need to harvest basic discovery and more efficiently accelerate the drug development process by aligning a diverse set of stakeholders in partnerships that included both traditional competitive and collaborative R&D efforts (Pfizer, n.d.). This construct has evolved to include a host of public-private partnerships aimed at improving the efficiency of translational science (World Bank, n.d.).

However, an R&D ecosystem for pandemic preparedness and response must address additional uncertainties and challenges. Scientifically, it is focused on products whose characteristics and ultimate purpose may not yet be known and may be developed for a market that may never exist. The manner in which such products may be designed for use can only be predicted in the abstract and may be intended for a time that may never arrive. While the needs can be imagined, the specifics cannot be known, requiring a new way of thinking about existing evidence, assessment of probabilities and a willingness to investigate and invest before the relevance of the evidence is clear.

Scientific advancements developed through the ecosystem can only lead to an effective epidemic response if they can be acted upon quickly. That requires not only a body of

relevant scientific information but also trained scientists, laboratories, development partners, trial networks, rapid funding and oversight, leadership and governance, all pre-positioned to act. Furthermore, effective continuity between *preparedness* R&D activities before an outbreak occurs and targeted R&D *responses* to the emergent pathogen afterward needs to be assured. The impact of the R&D process depends not only on the development of safe and effective products but also a means to manufacture them at a scale sufficient for pandemic needs and the mechanisms to finance and equitably distribute them wherever required.



There has been significant evolution of this ecosystem over the past decade, accelerated by the 2014-16 Ebola outbreak in West Africa. Notable progress can be found in the creation of global partnerships and mechanisms for new pre-pandemic or preparedness R&D, such as the development of One-Health approaches, the World Health Organization (WHO) R&D Blueprint, the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), the creation of the Coalition for Epidemic Preparedness Innovations (CEPI) and the prototype-pathogen approach that the National Institutes of Allergy and Infectious Diseases (NIAID) had taken to pandemic preparedness several years before the current outbreak (Marston et al., 2017).

In other words, over the course of a decade, the system has evolved from business as usual in pharmaceutical R&D to an enlarged R&D ecosystem, with industry involved in both competitive and collaborative research efforts, and then further to a new concept of an

R&D preparedness ecosystem. That is where the world was on January 1, 2020, shortly after the WHO was informed of a disease outbreak in Wuhan, China, that was causing severe pneumonia and respiratory failure, with a high case fatality rate. That turned out to be a novel coronavirus.

The existing preparedness ecosystem allowed R&D to shift rapidly in response. The sequence of the new virus was posted on January 11, 2020, and two days later scientists at the Vaccine Research Center of the NIAID decided to evaluate the spike protein of the virus and prepare the RNA sequence for an mRNA vaccine candidate, a vaccine platform they had been developing for several years in collaboration with the biotech company Moderna (Dance, 2020). Within a few days, the Vaccine Research Center team had synthesized the protein and examined its 3D structure to identify the most likely antigens to target with a vaccine, determined how to stabilize the structure, and engaged with Moderna to create the specific mRNA vaccine and begin studying the vaccine's ability to induce the host to synthesize the peptide and mount an immune response. Within six weeks, the first Phase 1 trials began.

Shortly before the sequence was posted, CEPI also began to mobilize its resources and partnerships to kickstart work with a variety of developers, including its existing vaccine R&D partners. With these and additional efforts from pharma and biotech, the number of vaccine development efforts focused on the new virus rapidly expanded, with a variety of approaches supported by different industry and academic groups and with various public sources of funding.

It is sometimes easy to overlook the fact that the R&D ecosystem in the United States has a number of fundamental differences from that of the rest of the world. As the response to COVID-19 — and before it H1N1 — illustrate, government funds support the bulk of the underlying science that goes into accelerated emergency vaccine development. For example, the NIAID and others support basic science, and the NIAID and the Centers for Disease Control and Prevention (CDC) support basic epidemiology; share virus specimens, animal models and laboratory resources; obtain the biological specimens needed to understand the immune response; and develop assays and diagnostics. Biomedical Advanced Research

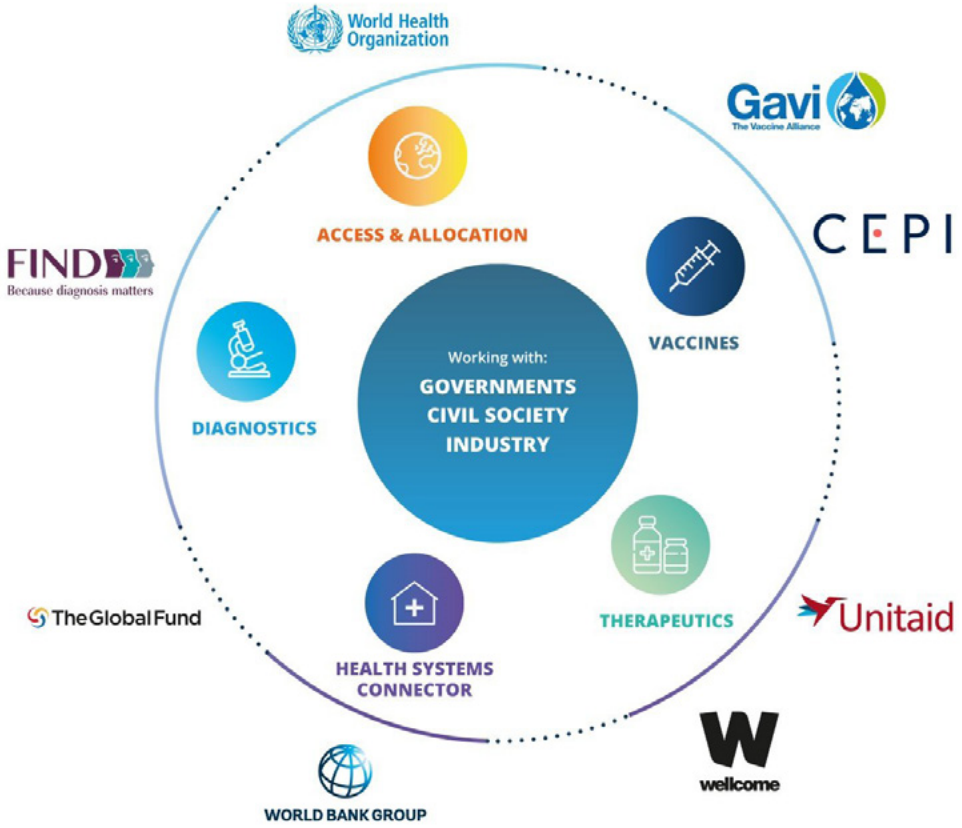
and Development Authority (BARDA) funding supports advanced product development (although emergency supplemental funds may be needed), as well as manufacturing at risk and at needed scale, and vaccine procurement for domestic needs. Finally, the CDC supports domestic vaccine distribution and a vaccination campaign.

As CEPI kicked off its vaccine development work, it rapidly confronted the fact that there were no pre-identified, go-to entities with the mandate, responsibility and funding to conduct the early enabling-science work — functions we take for granted in the United States. In other words, while the global scientific community is quite strong, there were no labs charged specifically with growing and sharing the virus with other labs and investigators, developing and supporting animal models, collecting and curating biological specimens, and so on. The ecosystem contained all these elements, but each depended on entrepreneurism and new funding to act. And, like a conductorless orchestra, each component played its part, often exceedingly well, but not always in a way to support an ideal tempo or harmony, or to eliminate needless repetition of movements. Despite these challenges, the extent of the global scientific collaboration has been staggering, and vaccine development has proceeded quickly both within the United States and, because CEPI had been established, outside it.

CEPI realized early that the requirements of the job would not be met once a successful candidate was developed. Yet no entity in the world had the mandate to support manufacturing the billions of vaccine doses needed in the face of a global crisis. Moreover, although industry has been heavily involved, it was not reasonable to expect the private sector to invest in manufacturing at risk and at scale without advance purchase commitments and financing to support the development and clinical trials of vaccine candidates. Similarly, there was no entity responsible for buying vaccine doses and distributing them globally and equitably in order to end the pandemic as quickly as possible.

Thus, the global ecosystem has had to adapt quickly. Global stakeholders came together to create the Access to COVID Tools Accelerator (ACT-Accelerator), which was launched on

April 24, 2020, and encompassed diagnostics, therapeutics, vaccines, personal protective equipment and health systems strengthening. Within it, the COVAX pillar, co-led by CEPI, Gavi and the WHO, is an attempt to link vaccine development, procurement and delivery in an end-to-end fashion. The COVAX facility, run by Gavi, is envisioned as a purchasing agent for both self-financed and subsidized country purchases. At the time of this writing, however, the COVAX partners were still struggling to raise the needed funding to support manufacturing scale-up and scale-out, advanced purchase commitments sufficient to incentivize manufacturing at risk, and dose procurement, as well as support of delivery to low- and middle-income countries.



Source: https://www.who.int/initiatives/act-accelerator/about

Meanwhile, high-income countries are engaging in multiple bilateral deals with manufacturers, threatening to drive up prices and compromise equitable global distribution. The lack of any system, let alone a strong day-to-day system, to ensure that vaccines are not only developed but also manufactured, distributed and delivered without delay should be clear to all. It is also evident that stopping the R&D ecosystem activities once a vaccine has

been shown to be safe and effective will not address the full scope of the challenge. The opportunity we have now is to develop a new paradigm — a unified, end-to-end R&D Preparedness and Response Ecosystem that begins with basic science and strong global disease surveillance and ends with vaccine administration sufficient to stop a pandemic. The question now turns from *whether to invest* in this to *how to connect the pieces*. That means identifying the effective ways to make connections at the same time that barriers are exposed and dismantled, overcome or bypassed. The challenges in manufacturing point to a part of the ecosystem that has continued to be neglected: innovation in manufacturing to simplify, speed up and de-risk the technical components of technology transfer and scale-out, as well as the manufacturing process itself. Early efforts through the WHO and PATH to do this for flu vaccine product formulation and sterile packaging (i.e., fill-finish) processes may serve as a model going forward (WHO, 2012).

We should note that a similar exercise has occurred in the development of therapeutic monoclonal antibodies. These are potentially of value to provide instantaneous passive immunity to a person exposed to a pathogen and to preclude infection in high-risk subjects, such as health care workers. They could also be useful therapeutically for individuals who are already infected and symptomatic or at an earlier stage to stop progression to clinical disease. A good example is the early decision by Regeneron to use its proven platform technology, which was successfully used to generate and then produce at scale humanized monoclonal antibodies to treat Ebola or prevent infection after exposure and is now being targeted at SARS-CoV-2. Shortly afterward, in early February, an existing collaboration with BARDA was extended to COVID-19 (Gallagher, 2020), and the NIAID subsequently co-funded clinical trials of the resulting product (National Institutes of Health, 2020). While such at-risk efforts are to be lauded, the risk exposure is of fundamental concern to pharma and biotech companies, and the R&D Preparedness and Response Ecosystem has to ensure that the funding to jumpstart development is in place.

WHAT IS THE NATURE OF AN R&D PREPAREDNESS AND RESPONSE ECOSYSTEM?

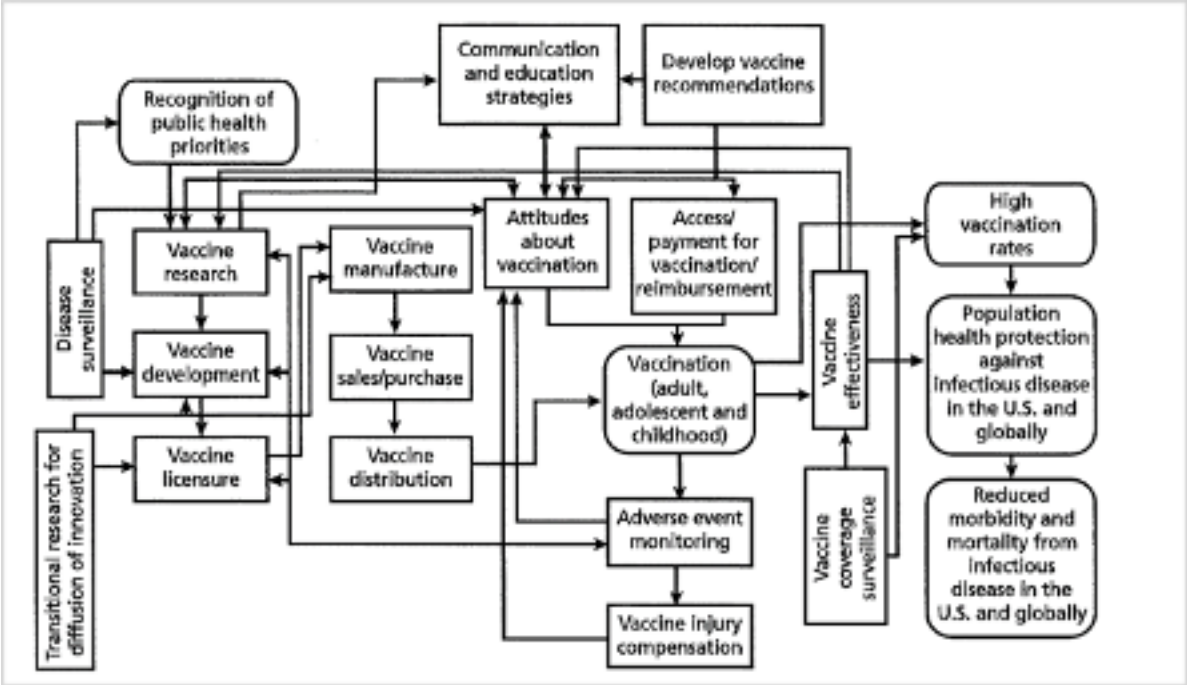
While we are of the mind that an end-to-end system is needed, starting with basic science and non-product-oriented research and stretching to the delivery of a vaccine to humans, that system is not necessarily linear. Indeed, to be responsive as fast as possible, it cannot be linear; many actions must be taken simultaneously.

This overarching ecosystem is made up of multiple smaller ecosystems, each functioning somewhat autonomously to identify and solve unique problems. Their activity levels may wax and wane as needs change, but each must always keep an eye on the others to determine when information sharing is going to be valuable or perhaps to actively overlap and partner, at least for some time. As a system of systems, the rules for connecting, partnering or operating in parallel are going to be fluid as demands evolve. They are also not predictable, at least not to the degree that traditional linear R&D in the private sector is required to be. That is surely a brake on ingenuity and invention, which makes the active management of the ecosystem something of a nightmare. Management is nonetheless essential, as we touch on shortly.

Because the ecosystem is clearly not two-dimensional, the usual organogram or process diagram drawn as a series of linked boxes (see Figure 1) cannot represent it, even if the various boxes can expand or contract over time as demands are altered. Because there is no way to predict where any of the parts are going to be in the future, the analogy becomes, in effect, more and more like quantum mechanics. It is also subject to Heisenberg's uncertainty principle, which posits that the momentum and position of a particle (analogous to a mini-system) cannot both be precisely determined at the same time, even in theory. Without the ability to use statistical methods to assess where these R&D particles are and how energized they are — because they cannot be clearly seen — how can they be managed?

While we are of the mind that an end-to-end system is needed, starting with basic science and non-product-oriented research and stretching to the delivery of a vaccine to humans, that system is not necessarily linear. Indeed, to be responsive as fast as possible, it cannot be linear; many actions must be taken simultaneously.

Figure 1. Overview of the vaccine and immunization enterprise



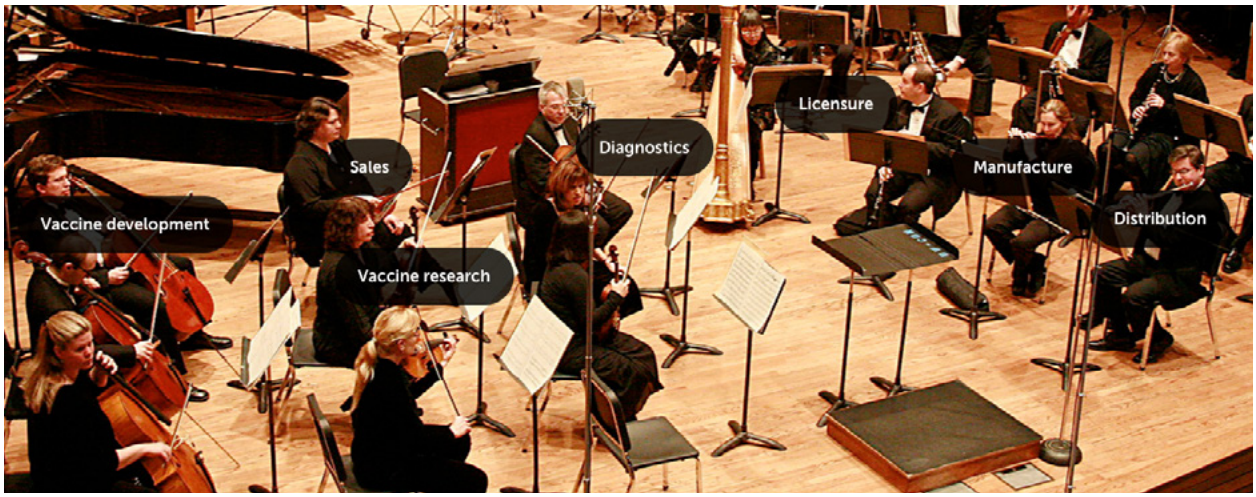
Source: Ringel et al., 2009.

The other analogy, mentioned above, is that of a conductorless orchestra composed of expert sections, including strings, brass, percussion and so on, preferably each with its own concertmaster. They are all in an empty auditorium and, depending on their orientation, may not see one another, a setup that becomes further complicated if the sections decide to move about (see Figure 2). We think there is value in coming to grips with these dynamic challenges in order to better align the parts and improve the outputs and the speed with which they can be developed. In this context, the principles of system dynamics may be of particular value.

The System Dynamics Society defines *system dynamics* as "a computer-aided approach to policy analysis and design. It applies to dynamic problems arising in complex social, managerial, economic, or ecological systems — literally any dynamic systems characterized by interdependence, mutual interaction, information feedback, and circular causality" (Systems Dynamic Society, n.d.).

The R&D Preparedness and Response Ecosystem has those fundamental characteristics: interdependence, mutual interaction, information feedback and circular causality. The challenge is to understand the parts and kinetics of the new ecosystem and how to guide the components to achieve the desired outcomes. Taking a system dynamics approach to this understanding might help elucidate a better governance approach for the preparedness-response ecosystem than we are able to propose here.

Figure 2. Each player represents a section of the orchestra or one mini-ecosystem of the whole



One of the planners of the Sabin-Aspen Vaccine Science & Policy Group asked whether the vaccine R&D ecosystem is a "wicked problem."

The question refers to the work of design theorists Horst Rittel and Melvin Webber, who used the term to characterize the complexities and challenges of describing social policy problems and planning solutions (Rittel & Webber, 1973). Compared to "tame" problems in mathematics or chess, "the wicked problems of planning lack clarity in both their aims and solutions...a challenge of articulation and internal logic, [and] they are subject to real-world constraints that prevent multiple and risk-free attempts at solving."

Rittel and Webber identify 10 important characteristics of wicked problems (see Table 1), which are similar to the challenges that system dynamics modeling attempts to solve. Importantly, the tenth characteristic states that planners — those who present solutions to these problems — have no right to be wrong. Unlike mathematicians, "planners are liable for the consequences of the solutions they generate; the effects can matter a great deal to the people who are touched by those actions."

Table 1. Characteristics of wicked problems

1. They do not have a definitive formulation.
2. They do not have a "stopping rule" and lack an inherent logic that signals when they are solved.
3. Their solutions are not true or false, only good or bad.
4. There is no way to test the solution to a wicked problem.
5. They cannot be studied through trial and error because their solutions are irreversible, so, as Rittel and Webber put it, "every trial counts."
6. There is no end to the number of solutions or approaches to a wicked problem.
7. All wicked problems are essentially unique.
8. Wicked problems can always be described as the symptom of other problems.
9. The way a wicked problem is described determines its possible solutions.
10. Planners, that is those who present solutions to these problems, have no right to be wrong. Unlike mathematicians, "planners are liable for the consequences of the solutions they generate; the effects can matter a great deal to the people who are touched by those actions."

Source: Stony Brook University, n.d.

To approach the management and governance of an R&D Preparedness and Response Ecosystem as a wicked problem may require broad-based and collaborative reasoning and help from system dynamics modelers to achieve focused future solutions. It will also need to evolve a management and governance structure that allows it to function freely and yet reins it in sufficiently to concentrate on practical solutions. Equally essential is how to organize and provide the required financial resources to make it work in a responsible manner. Even if not wicked, this is a tricky task.

WHAT CONDITIONS WILL ENERGIZE AN END-TO-END PREPAREDNESS AND RESPONSE ECOSYSTEM FOR R&D

Unless we believe the low-cost Albert Einstein thought-experiment approach will work here, an R&D Preparedness and Response Ecosystem will need substantial funding to meet its goals both before an outbreak and in response to one. To attract the necessary resources, it is essential to address the reluctance to invest before a pathogen proves its ability to cause

outbreaks, epidemics or pandemics. While investing in pathogen-agnostic antigen expression platforms is a good start, the prime barrier to early investment is that preparedness R&D research is scientifically focused on products whose characteristics, ultimate purpose and need are not yet known. As we commented earlier, the needs can be imagined, but the specifics are unknowable, requiring a new way of thinking about virulence and host-shifting capacity, assessment of the probability of future emergence and a willingness to investigate and invest before relevance is certain.

While continued early investments are key, situating those investments and capabilities as pre-positioned and globally distributed resources to respond to an emerging outbreak is critical. We propose that hubs for the core enabling scientific activities described in Table 2 be identified and positioned now. In most cases, there should be at least one hub per continent, both to promote equity in accessing scientific resources and because a novel pathogen can arise anywhere, although there are known hotspots for emergence. Standing capacity for this international research consortium could be collaboratively funded by scientific agencies around the globe.

Table 2. Core enabling activities and pre-identified, pre-positioned hubs

ENABLING SCIENCE ACTIVITIES	WHAT HAPPENED DURING COVID-19 PANDEMIC	PROPOSED R&D PREPAREDNESS ACTIONS
Posting and curating gene sequences throughout the pandemic.	Virus was sequenced privately weeks before being posted publicly and identified as a novel coronavirus. After initial posting on several sites, GISAID became central because it is the de facto go-to site for most of the scientific community. Largely maintained by volunteer scientists, GISAID received many more sequences than it could handle, and its funding was insufficient to function as needed.	Expand GISAID agreements to cover all viruses or establish a new and professional repository. Ensure adequate funding to curate pathogen sequences and maintain quality control. Consider a global treaty to reinforce need and commitment to early sequence posting and sample sharing for pandemic response.
Receiving, growing and sharing virus samples with laboratories around the world.	China did not make virus samples available. Once COVID-19 cases surfaced in other countries, several labs voluntarily grew virus and shared samples through their networks. However, no entity or network had a mandate or the necessary financial support for this. Nor was there an organized system with rules to prioritize requests for samples.	Pre-position and fund a global network of laboratories, at least one per continent, with the mandate and capability of receiving, growing and safely shipping virus specimens to investigators and product developers. Define the mechanism to vet and prioritize requesting entities.

ENABLING SCIENCE ACTIVITIES	WHAT HAPPENED DURING COVID-19 PANDEMIC	PROPOSED R&D PREPAREDNESS ACTIONS
Collecting, curating and disseminating human biological reference material.	Initially, collection of materials was opportunistic and unstandardized, and clinical samples were not necessarily appropriately stored. Validation panels for diagnostic tests are still in very short supply and often not standardized. No entities have a clear mandate or funding to take on these tasks. The National Institute for Biological Standards and Control (NIBSC), a WHO collaborating center, was funded by CEPI to develop antibody standards, but work was slow to start because of time lags in specimen collection.	Pre-position and fund a global network of investigators and laboratories, at least one per continent, with the mandate and capability of ethically collecting, managing and sharing specimens and curating standardized specimen collections.
Developing, validating and sharing animal models that replicate human disease progression, manifestations and pathology. Availability of containment laboratory and testing resources operating at international good laboratory practice standards or, under the Food and Drug Administration animal rule, well-controlled models and well-documented data.	Lack of immediate funding slowed animal model development and testing in labs that had available containment laboratory capabilities. Existing labs are at capacity and have struggled to keep up with demand.	Pre-position and fund a global network of laboratories and investigators, at least one per continent, with biosafety levels 3 and 4 capabilities. CEPI has recently funded such a network, but for vaccine development only. Invest in new technologies to reduce reliance on animal testing (e.g., organ-on-a-chip), and develop genetically engineered humanized mouse models tailored to the pathogen and human immune response.
Defining the basic epidemiology of the disease, with a focus on key knowledge gaps related to outbreak control and needs for product development.	Data collection was haphazard, poorly standardized and often inappropriately analyzed and published in pre-peer review platforms that were widely read and sometimes promoted unproven and potentially dangerous interventions. Modeling the course of an outbreak can only be as good as the quality of the data used in the model.	Strengthen International Health Regulations capacity in all countries, with capable and resourced national public health institutes closely linked to regional and global partners, including the active and proactive involvement of the WHO and partners.
Pre-position clinical trial networks with established adaptable protocols, ethical review standards and multi-site comparable and common quality-control methods in place for therapeutics and vaccines.	Numerous poorly designed, inadequately powered therapeutic studies with uninterpretable data. UK-based RECOVERY trial, launched in March 2020 and supported by the UK National Health Service (NHS) and others, a randomized controlled clinical trial to compare commonly available drugs as potential therapeutics across the whole NHS system. It rapidly recruited patients and generated conclusions. In April 2020 NIH launched its version, the Accelerating COVID-19 Therapeutic Interventions and Vaccines public-private partnership, for adaptive trials of promising treatments as well as vaccines. In March 2020 the WHO launched Solidarity, a multi-country adaptive therapeutics trial that has now produced interim results. No multi-arm studies for vaccines, as of yet.	Establish standing infrastructure and financing for randomized controlled multi-arm adaptive clinical trials for therapeutics and vaccines, with an objective, expert and flexible governance mechanism to coordinate protocol design, scientific and ethical review, selection of products to trial and patient inclusion criteria, outcome variables, safety monitoring, analysis and reporting.
Manufacturing scale-up and innovation.	Initially, no clear funding source for use or development of manufacturing capacity. High-income countries are buying up products in advance of approval for their own use ("vaccine nationalism") with simultaneous creation of global collaborative mechanisms to ensure products are available and subsidized for at-risk low- and middle-income countries, based on need and impact.	Pre-position and fund global network of manufacturing facilities for diagnostics, therapeutics and vaccines that can surge quickly to manufacture quality products in sufficient quantities. Promote manufacturing innovation to produce at required speed and scale faster. Develop new global mechanisms for product accession and fair distribution procedures, based on public health need and high potential to impact outbreak control.

Source: Keusch and Lurie analysis.

An operational expert research coordinating entity, potentially evolving from GloPID-R but with broader mandates for co-funding and the ability to move quickly, could be responsible for identifying and pre-positioning such implementing partnerships, encouraging equity of opportunity and recompeting and reevaluating the partnerships every five to 10 years. To be successful, pooled funding would also need to be pre-identified and available for release in a matter of weeks.

The World Bank's 2018 report, *Money and Microbes* (World Bank, 2018), suggested that a multi-donor fund held at the bank could support such activities, but other mechanisms may be similarly satisfactory. A key preparedness activity of the coordinating entity might be an annual, global scientific preparedness drill. Its purpose would be to strengthen global collaboration and capacity where outbreaks often originate and further the WHO's unique role in establishing norms for global behavior (e.g., data sharing, material transfer agreements, common protocols and ethics reviews) that can be leveraged in a pandemic.

When the full economic costs of the COVID-19 pandemic are calculated, it is certain they will far exceed the cumulative investment needed to put this R&D Preparedness and Response Ecosystem in place. Such a mechanism can preclude the enormous and ongoing loss of life and prevent the disruption of social, cultural, political and economic stability around the world. A major concern going forward is how to keep the sponsors involved for the long term; the examples of the U.S. government unilaterally exiting from multiple global compacts, including its decision to quit the WHO, are — in our minds — shortsighted, reprehensive and xenophobic.

Advancing global R&D preparedness with these early activities will also require a framework and threshold for activation (National Academy of Medicine, 2016). Not all outbreaks will become pandemics, and for this ambitious venture to be effective, there will be occasions when the global system and rapid expenditure mechanisms are activated and then quickly wound down because the outbreak is effectively contained, with minimal need for new countermeasures. Such a system is similar to the CDC's Influenza Risk Assessment Tool,

which evaluates the pandemic potential of novel influenza strains to provide guidance on how far into the vaccine development process the U.S. government should go.

The philosophy that one can always start the development process and then take an off ramp if the risk level is low enough also recognizes that it is impossible to make up for lost time. In this sense, rapid activation, a clear global good, should be viewed as a "cost of preparedness," akin to paying an insurance premium, but one that also builds capacity and provides the opportunity to practice for future events. Response to real-world events, when they occur, should be supplemented by research-response exercises to continually identify and overcome barriers. To be successful, a research-response fund would need a "no-regrets" annual budget to ensure that resources are always available and can be rapidly released, ideally within a week or two following a request. A sound objective mechanism for coordinating this effort is essential.

At the other end of the ecosystem, a different kind of financing is critical — a readily available reserve fund sufficient to support manufacturing at risk, procurement, distribution and administration of vaccine doses when a pandemic occurs. Estimates from the International Monetary Fund are that the global economy will take a $12 trillion loss in 2020-21 due to COVID-19; accelerating vaccine availability by a single month could save as much as $500 billion (Gopinath, 2020). Clearly, a reserve fund equivalent to even a week's losses of this magnitude would be a sound investment. The challenge now is for global leaders to muster the political will to mobilize the resources and design a governance structure for its use.

Meanwhile, vaccine development funders can continue to innovate in new technologies, from novel ways to stimulate B-cells to produce antibodies through next-generation, pathogen-agnostic vaccine development programs and innovations that will enable speedy, safe, light-footprint manufacturing capacity on each continent. Figuring out how best to conduct the remainder of the vaccine development symphony remains a tricky problem, if not a wicked one. New tools, such as system dynamics modeling, can meaningfully contribute to the solutions.

CENTRAL RELEVANCE OF PERIPHERAL ISSUES

Developing vaccines is a hardcore scientific process, to which formulation know-how, at times empiric rather than rational, is essential. It is not the place for amateurs to take on the highly critical responsibility for governance of the R&D Preparedness and Response Ecosystem of vaccines for future pandemic pathogens. Its leadership requires basic scientists,

formulation experience, translational research expertise and the ability to obtain licensure. Delivering vaccines to those who need them is another process issue, peripheral to vaccine development but essential to ensure that they are used at the population level. For new pandemic threats like SARS-CoV-2, that means at least 70 percent of the world's population, or whatever the threshold for herd immunity proves to be. Vaccine developers do not organize vaccine delivery, just as vaccine delivery experts do not develop them. But the effort and expense of development is futile if an effective vaccine sits on a warehouse shelf. This is what we mean by a centrally relevant peripheral issue.

All of that raises the question of the essential and proper role of the WHO in governance. The WHO is the only global public health institution for everybody — hence its name — and it serves a number of essential roles. One of the most important is to be the voice of those who are otherwise without one — people living in low- and lower-middle-income countries that often have poor health care systems and limited capacity to address population-level issues. The WHO must advocate for their concerns to the powerful and wealthy, who by and large dominate the scientific enterprise. The WHO is also the critical definer of normative standards for health and the defender of inclusive policies so that all at risk can benefit from medical advances, such as a safe and effective vaccine for COVID-19. As the race to develop this essential tool escalates, and vaccine nationalism rears up, the WHO is one of the few global entities that can convince and organize nations to take the moral high ground and promote equitable access. Again, this is an issue centrally relevant and yet peripheral to vaccine development.

Also centrally relevant, yet peripheral, is the availability of sensitive, specific, simple and speedy diagnostic tests. The efficacy of a vaccine cannot be tested if the pathogen cannot be identified among participants of rigorous controlled clinical trials who become ill. It is not the job of the vaccine developer to create these diagnostics, but it surely is necessary to their task.

The list can be extended to items such as personal protective equipment for health care workers and researchers caring for those potentially infected with the pandemic pathogen as part of clinical research and trials. As we have seen during COVID-19, the need extends to larger numbers of people doing work that may expose them to the virus, from grocery store clerks and delivery services to police and fire department personnel. Again, this is centrally relevant, but peripheral, to vaccine development.

We end this exercise in informed freethinking at this point. As the Sabin-Aspen Vaccine Science & Policy Group examines opportunities to advance the development of vaccines for pandemic pathogens like SARS-CoV-2 today, and others unknown tomorrow, in the most creative and hopefully audacious way possible, there are many relatively pedestrian issues to consider. We hope the group will advocate for the necessary support to build the broader end-to-end ecosystem we envision and believe is desperately needed. Equally essential is advocating for investments in high-risk/high-payoff new approaches to vaccine development and global funding mechanisms protected from precipitous failures due to sudden political shifts of key donor nations. Above all, having pulled out all the stops to achieve vaccine success, there must be a commitment to equitable access to a pandemic vaccine across the globe, regardless of a nation's ability to pay for it.

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UNDERSTANDING GLOBAL VACCINE ECONOMICS AND RESEARCH AND DEVELOPMENT

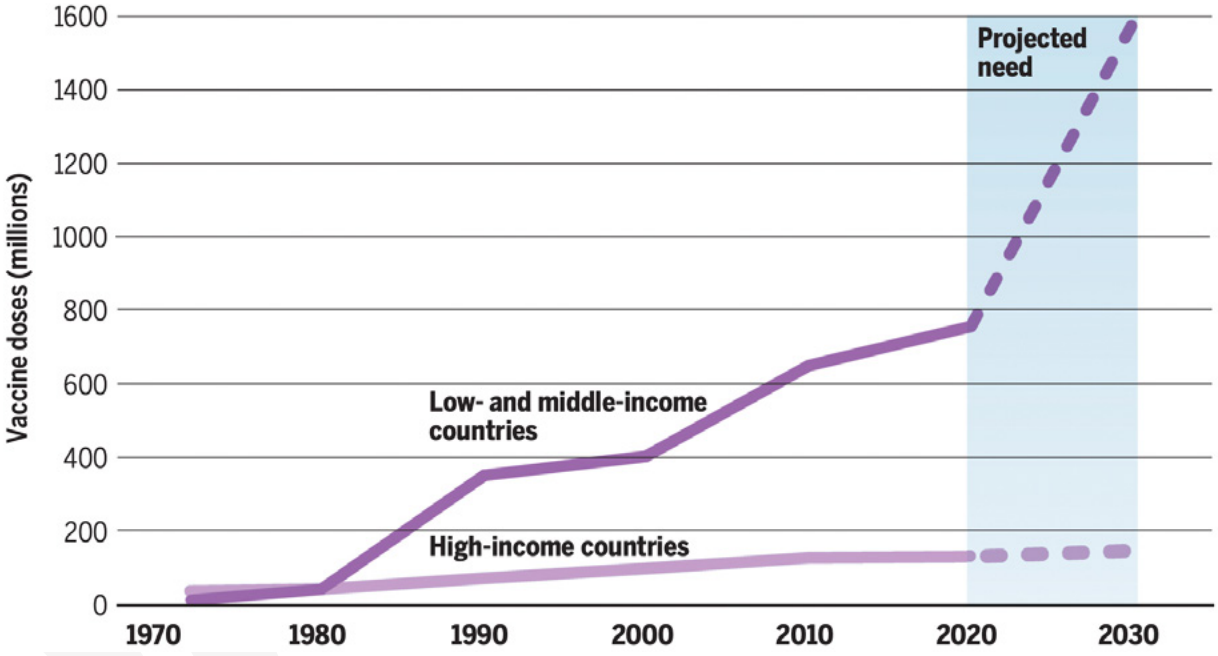
Jennifer Shulman, Rowena Ahsan and Kayleigh O'Malley

INTRODUCTION

Vaccines are among the most cost-effective ways to prevent morbidity and mortality from infectious diseases (Review on Antimicrobial Resistance, 2016) and have become the fundamental tool of the global public health community in the fight to improve health outcomes for the world's population.

The market for vaccines has grown considerably since the 1970s, primarily driven by the demand in low-income countries (LICs) and middle-income countries (MICs). Before COVID-19, the global vaccine market was expected to exceed $62 billion by 2027 (Top 10 vaccine manufacturers, 2020). Figure 1 shows the number of vaccine doses delivered globally from 1970 to the present, as well as the projected need from 2020 through 2030 (Rappuoli et al., 2019).

Figure 1. Vaccine doses by country income



Source: Rappuoli et al., 2019.

While it can be very profitable, the vaccine market is also extremely complex and interconnected, reflecting the difficulties of vaccine market research and development (R&D), the importance of intellectual property, and the intricacies of supply and demand that are created and influenced by vaccine market players. These vaccine market complexities have been further exacerbated in a world searching for a COVID-19 vaccine.

UNDERSTANDING VACCINE R&D

Vaccine R&D can cover several broad areas:

Research: The development of a new drug begins with a search for new chemical compounds, often drawn from large databases of known compounds and published information. Major international pharmaceutical companies typically have thousands of such chemical compounds within their R&D "pipelines" at any given time, including a variety of therapeutics and vaccines. At this stage in the process, preclinical research involves testing promising compounds in vitro and on animals in order to evaluate toxicity and to assess therapeutic potential.

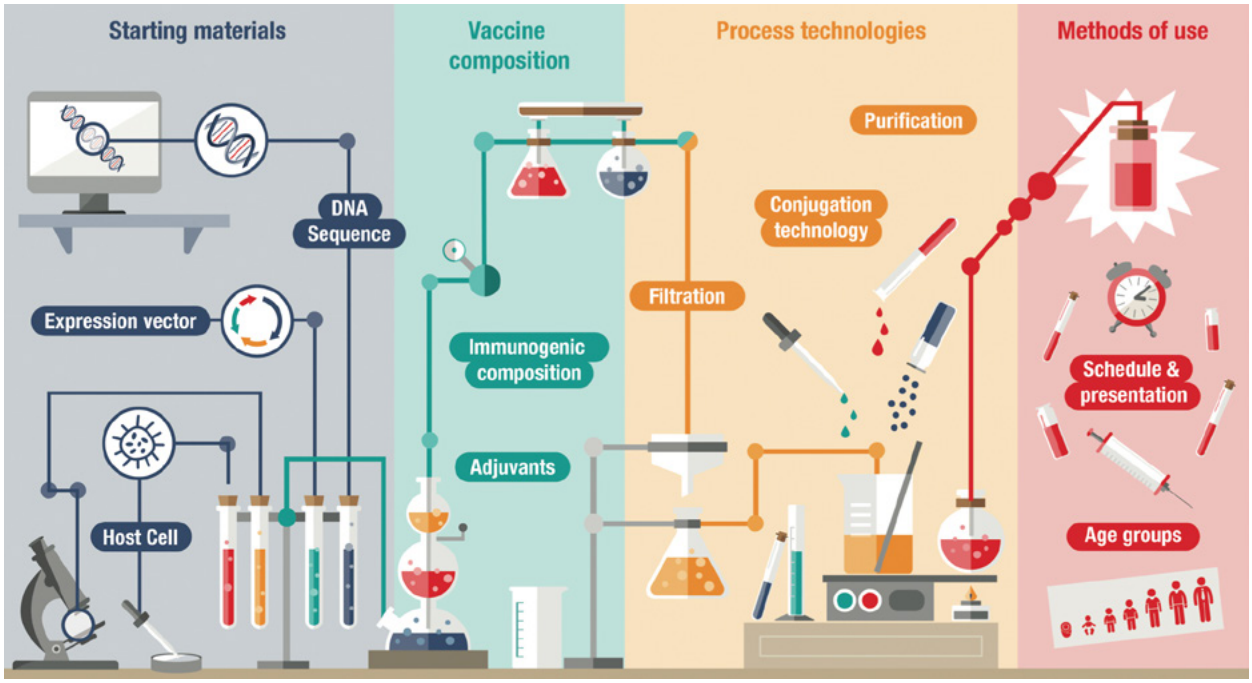
Development: After initial testing, manufacturers will generally patent a product and seek government permission to undertake human trials. The potential new drug compound then moves through various stages of clinical trials, which can often take several years. The clinical trial process includes several prelaunch phases with increasing numbers of healthy people, as well as postlaunch phases that are intended to strengthen the product's competitive position by developing data supporting efficacy and safety on a large scale. This process also allows manufacturers to develop an understanding of the correct dosing, including the appropriate age groups and dosing schedule.

Manufacturing: The manufacturing process is an important element for vaccine manufacturers, as vaccines are typically characterized as "biologics." Biologics are significantly more complex to manufacture than drugs (known as "small molecules"), as they are manufactured in living systems rather than through chemical synthesis. As a result, the manufacturing process for biologics must remain substantially the same over time, which requires extensive process control (Biotechnology Innovation Organization, n.d.).

This means that vaccine manufacturers require regulatory approval not only for the compounds themselves but also for their overall manufacturing process (see Figure 2 for an overview of the vaccine development process). Any changes in production, such as new

facilities, manufacturing equipment or raw materials, can trigger the need for new clinical trials to maintain licensure. Given the significant barriers to process improvement, vaccine manufacturers must have a high level of certainty about the manufacturing process early in the vaccine development life cycle (Plotkin et al., 2017).

Figure 2. Vaccine development process



Source: Médecins Sans Frontières, 2017.

A key feature of the global vaccine market is the significance of intellectual property. Unlike small molecule products, it is difficult to develop generic versions of biologics such as vaccines (called "biosimilars" or "bioequivalents") because a new manufacturer must demonstrate equivalence not only in the composition of the vaccine but also in the manufacturing process. Often, the only way to establish whether any differences impact the safety and effectiveness of the biosimilar is to conduct new clinical trials (Biotechnology Innovation Organization, n.d.). This difficulty in replicating manufacturing processes, along with stringent intellectual property rights in developed countries, tends to limit competition in the vaccine market and create higher prices and supply vulnerabilities. While some mechanisms exist in the industry to enable information sharing, such as licensing arrangements and redesigning manufacturing processes, these efforts can be costly and time intensive (Médecins Sans Frontières, 2017).

In general, vaccine R&D is a difficult endeavor for manufacturers for two reasons:

- **The chance of success is low.** As of Q1 2020, the Massachusetts Institute of Technology estimates the probability that a vaccine will move from conception to Phase 3 trials is 39.8 percent (Project ALPHA, n.d.).
- **The process is long.** Pharmaceutical Research and Manufacturers of America estimates that in the United States, it can take more than 10 years to develop a novel vaccine, with only 12 percent of products that enter clinical trials ultimately approved for the market (America's Biopharmaceutical Companies, 2020).

Combined, these two factors create a significant financial risk for vaccine development. As with most high-risk investments, the motivation is a high return on investment. The importance of reward becomes clear in this paper's later discussion of the two distinct vaccine markets: developed markets and developing markets.

Aside from the obvious risk of dedicating resources that do not yield a viable vaccine, there are more subtle risks associated with vaccine R&D, including demand. The quest for an HIV vaccine is an enlightening example. Although the virus was identified in the 1980s and has claimed 33 million lives, there is still no HIV vaccine on the market (World Health Organization [WHO], 2020e). One reason is the unique challenges associated with HIV, including the lack of natural immunity, the frequency of mutation, an indeterminate immune response and lack of animal models (The History of Vaccines, n.d.). An additional factor is that while some scientists have been working on vaccine options, others have made enormous progress in developing tools to prevent or treat HIV treatments, including life-saving antiretrovirals that limit the risk of transmission and pre-exposure prophylaxis (U.S. Department of Health and Human Services, 2020). While transmission has not stopped, these therapeutic advances have changed priorities. Even if a successful HIV vaccine reaches the market in the future, sales will likely be limited, giving vaccine manufacturers less incentive to continue investing resources here.

UNDERSTANDING SUPPLY: A TALE OF MANUFACTURERS

The vaccine market is characterized by significant barriers to entry, including high development and production costs, high failure rates, the need for high levels of competence and expertise, and lower revenues and profitability compared to the drug market. These barriers mean the number of manufacturers able to enter the vaccine market remains low.

The market for each vaccine has become so consolidated that many can now be described as monopolies or oligopolies; 32 percent of vaccines have fewer than four suppliers, and 63 percent have two or fewer suppliers that are prequalified by the WHO or UNICEF (WHO, 2018). This section explores in further detail the supply implications of these market failures.

THE ECONOMICS OF THE VACCINE MARKET

Vaccine development and production are costly and capital intensive. Manufacturers require large-scale production and long product life cycles to produce at low cost, recover their sunk and fixed costs and earn a reasonable return on investment. Sunk costs in relation to R&D, facilities and equipment are incurred in the upfront investment stages of vaccine development and in preparing for production. Other direct and indirect costs, which can be fixed or variable in nature, are typically incurred once production has begun.

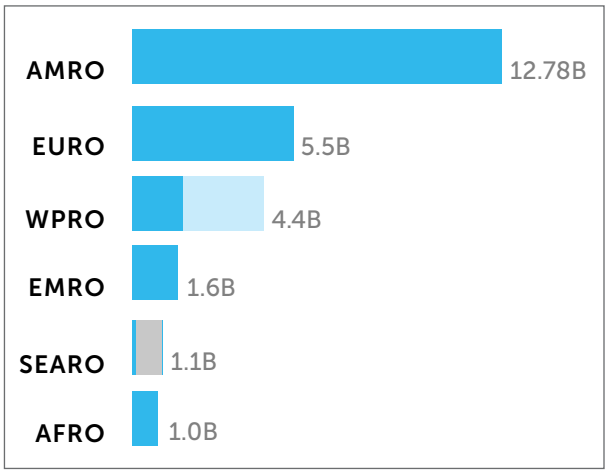
Historically, many vaccines were developed for a dual vaccine market (i.e., one targeting both developed and developing countries) (WHO, 2018). In that situation, the financial returns associated with high-income countries (HICs) have been sufficient to justify the commitment to vaccine development and provision of low-cost vaccines to LICs and MICs. Vaccine manufacturers made most of their profits in HICs, recouping their investment and production costs, and could sell the same vaccines at lower prices to countries with fewer resources. This model, however, has recently become more complicated as vaccine manufacturers engage in developing vaccines that lack a dual market. For example, vaccines against the Ebola and Zika viruses and for endemic diseases that are present predominantly in LICs and MICs, such as malaria and tuberculosis, lack the financing mechanism for dual-market vaccines. As such, vaccine manufacturers are looking for new ways to recoup their investments.

When planning production to supply multiple markets, manufacturers must also consider the competitive landscape and what market share is realistic and sustainable, as well as whether they will be able to compete based on their costs. They are unlikely to invest in new vaccines if they cannot foresee the opportunity to recoup their research, development and production costs, as even a company with a strong social commitment must answer to its shareholders. Indeed, in January 2018, three of the five major vaccine manufacturers announced that the world should not count on them to develop vaccines with no return on investment (Rappuoli et al., 2019).

MARKET SIZE AND CONSTRAINTS

The WHO estimated that the global vaccine market was worth approximately $26 billion in 2018, a 25 percent increase from the prior year. Nearly 70 percent of this value (defined as revenue in dollar terms) was generated in the Americas and the European region, with countries in the Western Pacific, Eastern Mediterranean, Southeast Asian and African regions accounting for the remaining 30 percent of the market (see Figure 3) (WHO, 2019b). But dollar values paint an incomplete picture of the global vaccine markets. Exploring the disparities between developed and developing countries more clearly highlights the imperfections in the vaccine market and provides insight into the motivations of vaccine manufacturers serving countries at different income levels.

Figure 3. Global value by region



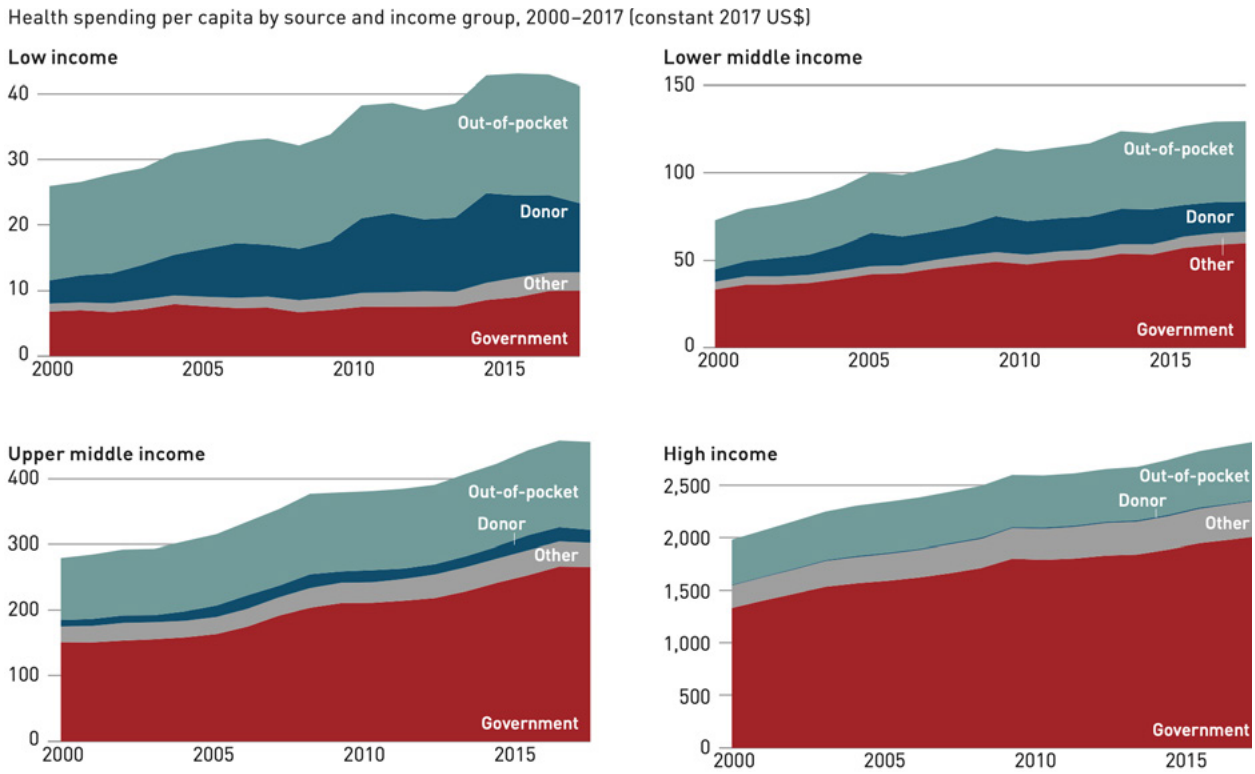
Source: WHO, 2018.

- **HICs** constitute **82 percent** of the global vaccine market in terms of dollar value, but only about **20 percent** of the annual volume of vaccines consumed (i.e., vaccine demand).
- **LICs** and **MICs** together account for about **18 percent** of the dollar value of the global vaccine market but approximately **80 percent** of the annual volume (WHO, 2018).

In this section, we discuss some of the core features of the vaccine market that drive this difference between dollar value and volume.

HICs spend more on health than LCIs. While government spending on health has grown everywhere over time, the spending in HICs continues to significantly outpace that of LICs and both lower- and upper-MICs (see Figure 4). Health spending in HICs and upper-MICs is also dominated by government spending, while lower-MICs and LICs rely much more on out-of-pocket expenses and donor funding. Given the dollars at play in HICs and the deep pockets of governments in these countries, it is unsurprising that these markets are more attractive to vaccine manufacturers.

Figure 4. Breakdown health care spending per capita by country income group

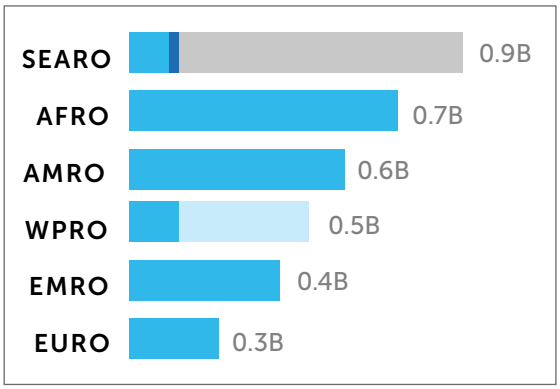


Source: WHO, 2019a.

Vaccine uptake is consistently high in HICs. Based on WHO-UNICEF data, the average uptake of vaccines globally varies between 39 percent for rotavirus and 90 percent for the first dose of diphtheria, tetanus and pertussis (DTP1) in 2019 (WHO, 2020d). However, these averages mask extreme disparities between regions; for example, the DTP1 coverage in most developed countries is above 90 percent, but many developing countries in Africa and Southeast Asia have coverage of less than 60 percent (UNICEF, 2020). This is partly driven by the disparity in health spending across countries with differing incomes.

The dollars and the volume tell very different stories. As noted earlier, the revenue for vaccine manufacturers tends to be generated in HICs, including North America and Europe, a marked contrast to the volume of vaccines consumed (see Figure 5). The WHO estimates that of the 3.5 million doses of vaccines consumed in 2018, the largest volumes were in the Southeast Asian and African regions, which together accounted for 45 percent of the global total. The Americas and European regions together accounted for only 26 percent of the market (WHO, 2019b).

Figure 5. Global volumes by region

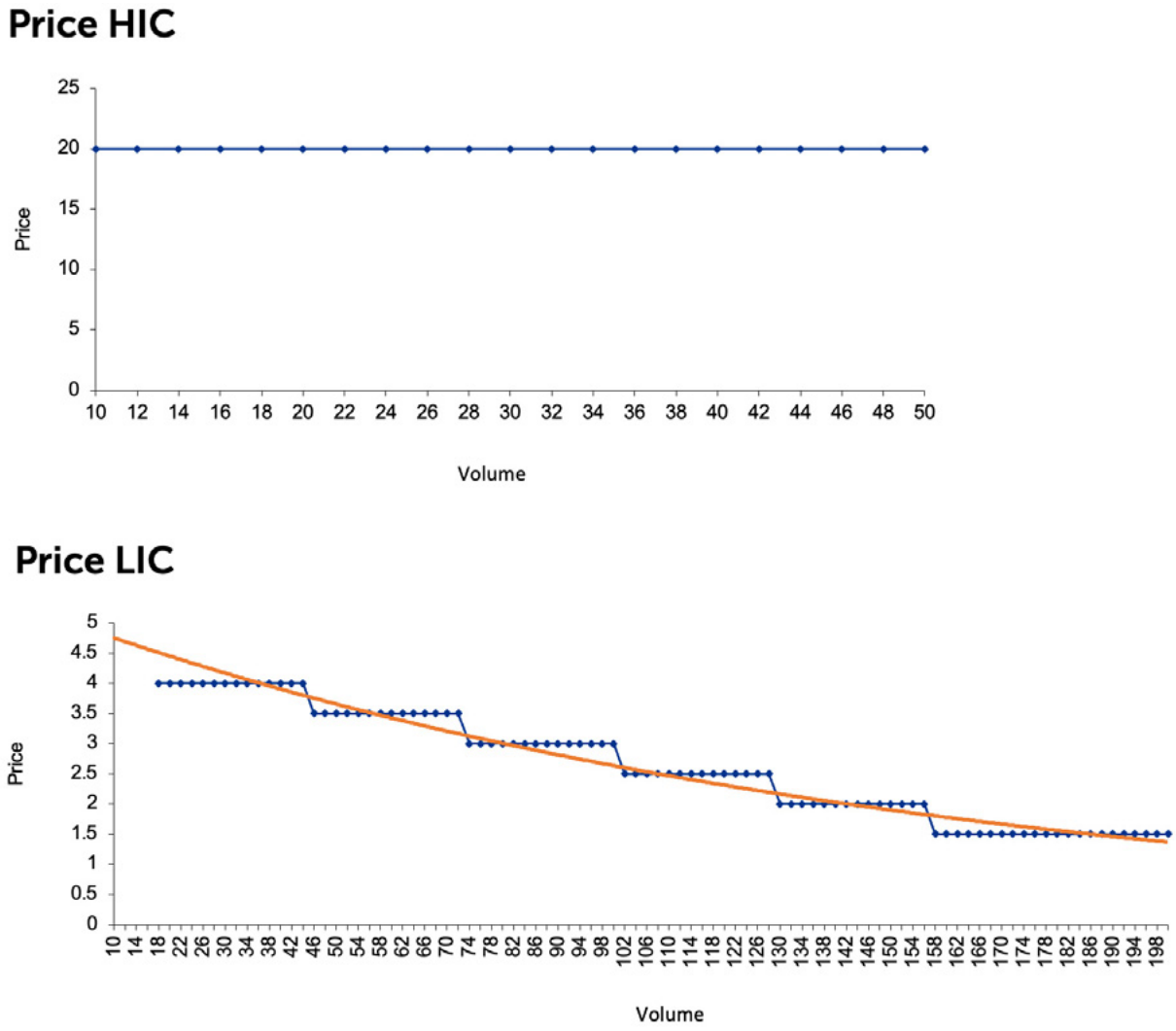


Source: WHO, 2018.

The result is that even with relatively lower vaccine uptake, population differences result in much higher demand in low-income and middle-income countries compared to high-income countries, yet those former markets are underserved. To understand the market, there is one more critically important factor: price.

Vaccine manufacturers receive much higher prices for their products in some markets and for particular types of products. The WHO notes strong evidence of price tiering based on income level, with HICs paying prices that are more than five times higher than MICs on average (see Figure 6) (WHO, 2019b). At the same time, it is important to note inconsistencies in this pattern for individual countries and specific vaccines. Although there is less demand in HICs, they are more profitable for vaccine manufacturers.

Figure 6. Vaccine price and volume: Comparing the markets



Source: KPMG Economic Services, 2020.

Product type is another key point of price differentiation. While the traditional vaccines delivered to LICs and MICs continue to drive global market volume, the innovator vaccines that are primarily distributed in HICs drive global market value, largely due to the premium prices vaccines command there (WHO, 2018).

The priorities of vaccine manufacturers and public health are misaligned. In an environment subject to purely market forces, a rational vaccine manufacturer would have every incentive to prioritize the needs of HICs over those of LICs and MICs.

This is illustrated with a hypothetical example of a multinational vaccine manufacturer that has developed two vaccines but only has enough production capacity to supply one of them (see Table 1). Vaccine A provides protection against a disease with moderate symptoms that is not life-threatening and impacts 100,000 individuals globally. Vaccine B provides protection against a disease with severe symptoms that is life-threatening and impacts 1 million individuals globally. From a public health perspective, Vaccine B should clearly be the priority. In reality, this is not always the case.

Table 1. Comparing vaccines: Where the profits lie — a hypothetical

	VACCINE A	VACCINE B
Disease profile	Moderate symptoms; not life threatening	Severe symptoms; life threatening
Potential recipients	100,000	1,000,000
Average price per unit	$200	$2
Revenues generated	$20,000,000	$2,000,000

Source: KPMG Canada.

The key motivation for vaccine manufacturers, as with all companies, is to maximize shareholder value, which is traditionally done by maximizing profit. Whether the "shareholder" is the owner of stock in a public company or a family that owns a privately held corporation, profit remains paramount. With respect to vaccines, there are two ways to achieve this result: higher prices with lower volumes or lower prices with higher volumes. In the example above, if the potential recipients of Vaccine A are in HICs, where the product can be sold for $200 per unit, no rational manufacturer would opt to dedicate its resources to Vaccine B, which can only be sold for $2.

This example illustrates the fundamental flaw in the vaccine market, in which LICs and MICs are underserved and HICs are prioritized. This is not to imply that multinational manufacturers do not supply LICs and MICs but rather that multinational manufacturers focus largely on the wealthier nations. As a result, since the 1980s, manufacturers from emerging markets have entered the market. These companies, collectively referred to as the Developing Countries Vaccines Manufacturers Network (DCVMN), play an increasingly important role in getting vaccines to LICs and MICs, supplying 55 percent of the doses

procured by Gavi, the Vaccine Alliance (Gavi) between 2012 and 2018 (Pagliusi et al., 2020) and 50 percent of the doses procured by UNICEF in 2017 (Hayman and Pagliusi, 2020).

Market dynamics for multinational vaccine manufacturers are very different from those of the DCVMN companies. The volume and price available to the markets they serve vary considerably, creating two distinct sets of incentives. As noted, multinationals tend to prioritize HICs with lower volumes and higher prices, while DCVMN companies operate almost exclusively in the high-volume, low-price environments of LICs and MICs. Where similar products are supplied by both types of manufacturers, the prices charged by multinationals have historically and consistently been higher than those charged by DCVMN companies (WHO, 2019b).

MULTINATIONAL VACCINE MANUFACTURERS

Four major players — the Big Four — currently dominate the global vaccine market: GlaxoSmithKline, Sanofi, Pfizer and Merck. The list of top 10 companies is rounded out by Novartis (Switzerland), as well as biotechnology companies Emergent BioSolutions (U.S.), CSL (Australia), Inovio Pharmaceuticals (U.S.), Bavarian Nordic (Denmark) and Mitsubishi Tanabe (Japan) (Fortune Business Insights, 2020).

The Big Four corporations generate 80 percent of global vaccine revenues (WHO, n.d.). Beginning in the 1970s, significant market consolidation reduced the vaccine manufacturing market from 20 companies to a handful of large ones (Kaiser Health News, 2020). For example, GlaxoSmithKline has undergone approximately six mergers and acquisitions since 1995: Wellcome (1995), Smithkline Beecham (2000), Block Drug Co. (2001), Stiefel (2009), Novartis global vaccine business (2015) and Tesaro (2018) are now all part of the corporation (GlaxoSmithKline, n.d.-a). In addition to large mergers, these dominant players have acquired a number of smaller biotech companies, such as AstraZeneca's acquisition of Cambridge Antibody Technology, MedImmune, Spirogen and Definiens (AstraZeneca PLC, 2020).

These companies generally manufacture portfolios of vaccines, including "blockbuster" vaccine products, as well as a variety of other pharmaceutical and life science products.

Blockbuster vaccines are defined as vaccines that generate more than $1 billion annually. The Big Four hold a significant amount of intellectual property and engage in constant R&D and innovation for new vaccines, as well as improving on existing vaccines and manufacturing practices. In general, multinationals apply a portfolio approach by investing in multiple vaccine candidates and other pharmaceuticals concurrently. By working with a mix of early-stage and late-stage products, they can diversify their risks, maximize use of their manufacturing and distribution networks and smooth out their cash flows over time. However, the degree to which multinational pharmaceutical companies can leverage a portfolio approach depends on their size and extent of financial resources. For example, GlaxoSmithKline boasts a portfolio of over 30 vaccines, with another 15 vaccines in its pipeline (GlaxoSmithKline, n.d.-b, n.d.-c), while Emergent BioSolutions has a portfolio of four vaccines, with another seven in the pipeline (Emergent BioSolutions, n.d.-a., n.d.-b.).

The conventional wisdom is that profits generated from existing operations (both vaccine and nonvaccine) are a key source of R&D funding (Garnier, 2008). In fact, global R&D spending by pharmaceutical companies was estimated to be $179 billion in 2018, with projected growth to $213 billion by 2024 (Evaluate Ltd., 2019). These funds can be directly invested into growing their own pipelines or used to buy a pipeline of new products by acquiring competitors or small startups with promising pipelines. By increasing investments in innovative, small companies, larger pharmaceutical companies can avoid direct spending on new drug development while maximizing use of their sales and marketing infrastructure (Robinson, 2020).

Small biotechnology companies and startup vaccine manufacturers provide the vaccine industry with innovation. The small biotech companies represented 31 percent of new molecular entities registered with the U.S. Food and Drug Administration (FDA) in 2009, a number that grew to 64 percent by 2018 (Robinson, 2020). Such companies are initially funded by venture capital firms or other private investors, but that funding does not always last. These organizations tend to have a very specialized focus on one or a few products but often lack the revenues or margins to generate any scale or gain market share. Generally, the larger companies with deeper pockets are better equipped to translate the innovations of smaller companies into saleable products.

Increasingly in pursuit of profitable, inorganic growth opportunities, larger companies strategically acquire startups and midsize companies to broaden their portfolios of products and services. For example, in February 2019, Bharat Biotech acquired Chiron Behring Vaccines, a clinical biotechnology company and one of the leading manufacturers of rabies vaccines around the globe (Research and Markets, 2020). Similarly, in 2017, Takeda Pharmaceutical acquired ARIAD Pharmaceuticals, which specializes in cancer medication (Research and Markets, 2020), while Sanofi acquired Shantha Biotechnics, a producer of recombinant human health care products in India (Sanofi-Aventis buys Shantha, 2009), and Protein Sciences, which develops vaccines and biopharmaceuticals against influenza and other diseases (Research and Markets, 2020).

In addition to the private market, the pharmaceutical industry draws heavily on government sources, such as the U.S. National Institutes of Health (NIH). Research indicates that every one of the 210 new drugs approved by the FDA between 2010 and 2016 received some level of NIH funding, with total funding in excess of $100 billion (Cleary et al., 2018). Another source for global pharmaceutical R&D operations are beneficial tax credits in various countries. For example, Australia offers refundable R&D tax offsets between 38 percent and 43.5 percent of costs incurred (Zehr, 2018).

Table 2 summarizes the differences between multinational vaccine manufacturers and small biotech companies.

Table 2. Vaccine manufacturers at a glance

COMPANY TYPE	LARGE VACCINE MANUFACTURERS	SMALL BIOTECHNOLOGY COMPANY
Product Portfolio	Diversified	May be diversified or undiversified
Market	LICs, MICs and HICs	Not applicable: typically in precommercial phases and unlikely to generate any scale or gain market share
Margins	High	Not applicable: typically in precommercial phases and unlikely to generate any scale or gain market share
Source of R&D Funding	• Profit from other products • Shareholder or government investment	Shareholder or government investment
R&D Strengths	Funding options	R&D productivity
R&D Weaknesses	R&D productivity	Funding options

Source: KPMG Canada.

DEVELOPING COUNTRY VACCINES MANUFACTURERS NETWORK

The DCVMN, established in 2000, is a public-health-driven, international alliance of manufacturers from developing countries (DCVMN, n.d.). There are now more than 40 vaccine manufacturers in the DCVMN across 14 countries, predominantly based in India and Southeast Asia, with some manufacturers in Brazil and Africa. As the multinational vaccine manufacturers continue to turn their attention away from the lower-price low-income and middle-income markets, the DCVMN helps to ensure a consistent supply of traditional, lower-cost vaccines to developing countries, playing an increasingly important role in that supply. DCVMN vaccines comprised approximately half of UNICEF's 2017 procurement supply by volume (Access to Medicine Foundation, 2017) and 55 percent of Gavi's procurement supply by volume between 2012 and 2018 (Pagliusi et al., 2020).

R&D is as pressing an issue for DCVMN companies as it is for the multinationals. As of October 2019, DCVMN companies reported 181 vaccine projects in the R&D pipeline, 24 of which were for novel vaccines and 41 of which were in the last phases of clinical development. This compares to only 11 vaccines reported in late development stage in 2011 (Hayman & Pagliusi, 2020).

Unsurprisingly, the R&D conducted by DCVMN companies is much less intensive than the R&D activities of their multinational counterparts; for example, the R&D-to-sales ratio for the Big Four ranged from 14 percent to 22 percent from 2015 to 2019, compared with two percent to 16 percent for a sample of DCVMN companies during the same time period (on a much smaller revenue base).

Unlike multinationals, DCVMN companies are unable to rely as heavily on self-funding for their R&D investments, partly because of lower vaccine prices in LICs. Additionally, they typically do not have the product diversity or global sales networks to match the revenue-generating power of their multinational counterparts. As a result, they rely more heavily on volume to generate revenue, either through domestic procurement in their respective countries or international programs, such as the WHO or UNICEF prequalification.

As an alternative to self-funding, DCVMN companies rely much more heavily on public funding and blended public-private sources. Examples include milestone-based grants from the Coalition for Epidemic Preparedness Innovations (CEPI); loans, project financing or volume guarantee funding vehicles from organizations such as the Bill & Melinda Gates Foundation; and loans, equity and project financing from impact-investing funds, such as Adjuvant (Pagliusi et al., 2019).

The distinctions between large and small DCVMN companies are highlighted in Table 3.

Table 3. DCVMN companies at a glance

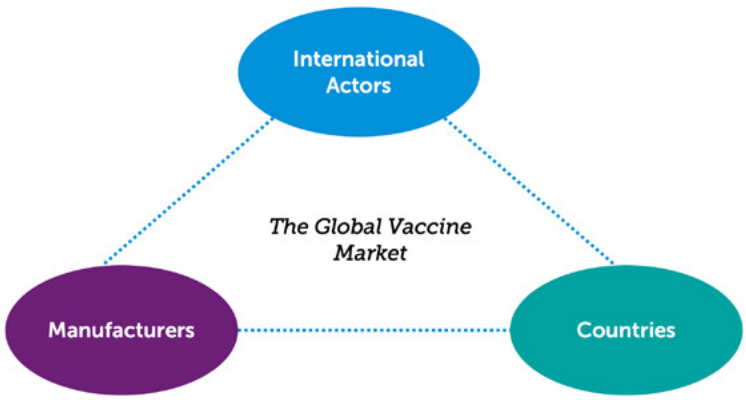
COMPANY TYPE	LARGE DCVMN COMPANY	SMALL DCVMN COMPANY
Product Portfolio	Diversified	Undiversified
Market	LICs and MICs	LICs and MICs
Margins	Low	Low
Source of R&D Funding	• Government investment • Public-private partnership investment	• Government investment • Public-private partnership investment
R&D Strengths	Funding options	R&D productivity
R&D Weaknesses	R&D productivity	Funding options

Source: KPMG Canada.

UNDERSTANDING DEMAND: SHAPING THE ECONOMICS AND FINANCING OF THE VACCINE MARKET

Vaccine demand is created by countries, but much like the supply side of the market, it is influenced by two differing sets of economic circumstances: those prevalent in HICs and those in LICs and MICs. As well, another group of players needs to be considered: nongovernment, nonprofit international organizations that influence the vaccine market through procurement policies and funding mechanisms (a broad group we label "international actors" in this report) (WHO, n.d.). Importantly, each of these players impacts the others (see Figure 7).

Figure 7. Key players in the global vaccine market



Source : KPMG Economic Services, 2020.

A healthy and sustainable vaccine market provides the right balance

between supply (determined by vaccine manufacturers) and demand (determined by countries). International actors, the third player in this system, can impact both supply and demand, depending on the market tools used. On a global basis, the vaccine market has not reached a state of stability or equilibrium, and in many cases, vaccine security is still a concern.

THE ROLE OF COUNTRIES

The vaccine market in HICs functions reasonably well without material government intervention because the price commanded by vaccine manufacturers is enough to drive innovation and meet market demands. In those countries, government intervention is used to ensure sufficient uptake of vaccines; for example, in the vast majority of Organisation for Economic Co-operation and Development countries, the coverage for both the DTP and the measles vaccine exceeds 90 percent (Organisation for Economic Co-operation and Development, n.d.).

The story is very different in LICs and MICs. The WHO estimates that in 2019 14 million infants did not receive an initial dose of the DTP vaccine and that an additional 5.7 million were only partially vaccinated. Approximately 60 percent of these children live in 10 countries: Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Mexico, Nigeria, Pakistan and the Philippines (WHO, 2020a). There are several reasons for this gap.

Government health care spending in LICs and MICs is significantly lower than in HICs (see Figure 4). In some cases, this may be driven by conflict or disease outbreaks that prevent sustainable and consistent delivery of services. For example, in 2019, an estimated 14 million infants were still not reached by vaccination services (UNICEF, 2020). While insignificant

globally (representing only 0.2 percent of total global health spending), funding from international donors continues to be important for LICs (accounting for 27 percent of health spending) and MICs (accounting for 3 percent of health spending) (WHO, 2019a).

The characteristics of a vaccine, such as thermostability, number of doses required and the serotypes targeted, can also have a significant impact on how immunization programs can be effectively implemented in low-resource settings (Access to Medicine Foundation, 2017). It may not be possible to effectively administer vaccines in LICs and MICs that are a routine part of the immunization programs of HICs.

Finally, in addition to the market incentives for vaccine manufacturers to favor HICs, supply stability continues to be a challenge for LIC and MIC markets, with frequent stockouts or stock disruptions. The impact of stockouts can be felt for several months, and only some of the lost demand is recovered (Gooding et al., 2019).

THE ROLE OF INTERNATIONAL ACTORS

The lack of financial incentives for vaccine manufacturers, especially multinational ones, to adequately engage in R&D and provide vaccines to LICs and MICs poses challenges that resource-strapped governments cannot address on their own. As a result, a strong network of international organizations operates in the LIC and MIC vaccine markets. These organizations use a variety of mechanisms to shape the economics and financing of the vaccine market.

INTERNATIONAL PROCUREMENT

Pooled procurement is a popular tool to generate the volume needed to attract manufacturers. Individual LICs and MICs rarely have the market power or funding to influence the decision making of vaccine manufacturers, especially multinational corporations. To bypass this constraint, a number of multilateral procurement agencies undertake vaccine procurement on their behalf (see Figure 8). Three of the largest procurement agencies are UNICEF's Supply Division, Gavi and the Pan American Health Organization (PAHO) Revolving Fund. Each year, these organizations supply billions of doses of vaccines to LICs and MICs around the world.

Figure 8. Price per dose by procurement group

	UNICEF (Gavi)	UNICEF-procuring MICs	PAHO RF	Self-procuring MICs	Self-procuring HICs
BCG	0.11	0.11	0.21	0.20	1.03
bOPV	0.14	0.14	0.15	0.22	0.27
DT	0.16	0.16	0.17	0.35	4.00
DTaP			15.00		14.65
DTaP-HepB-Hib-IPV			20.60	29.52	35.89
DTaP-Hib-IPV			14.20	22.20	26.61
DTaP-IPV			11.50	16.69	20.58
DTwP	0.22	0.22	0.17	0.22	3.82
DTwP-HepB-Hib	0.87	0.87	1.08	1.20	4.96
HepA			10.66	9.59	21.02
HepB	0.27	0.27	0.24	1.40	5.73
Hib			2.05	5.16	9.50
HPV	4.55	13.57	9.04	11.59	50.92
IPV	1.68	2.38	3.65	4.99	8.53
JE	0.41			0.76	10.43
Measles	0.31	0.31		0.90	
MenACWY			20.30	21.17	30.73
MMR	2.50	2.50	3.26	5.65	7.54
MR	0.73	0.73	1.43	0.86	
OCV	1.60	1.60	1.85		20.04
PCV	3.09	14.00	13.68	22.76	45.35
PPSV			7.98		18.93
Rabies			12.80	7.90	20.67
Rota (per course)	7.15	8.00		18.82	41.49
Seasonal Influenza		3.75	2.94	3.32	6.75
TBE				5.35	18.34
Td	0.12	0.12	0.09	0.27	11.43
Tdap			11.47		17.88
TT	0.09	0.09		0.32	3.22
Typhoid Ps				10.83	10.29
Varicella			14.46	24.01	25.02
YF	1.15	1.15	1.35	18.94	20.04

Source: WHO Global Vaccine Market Report, 2019b.

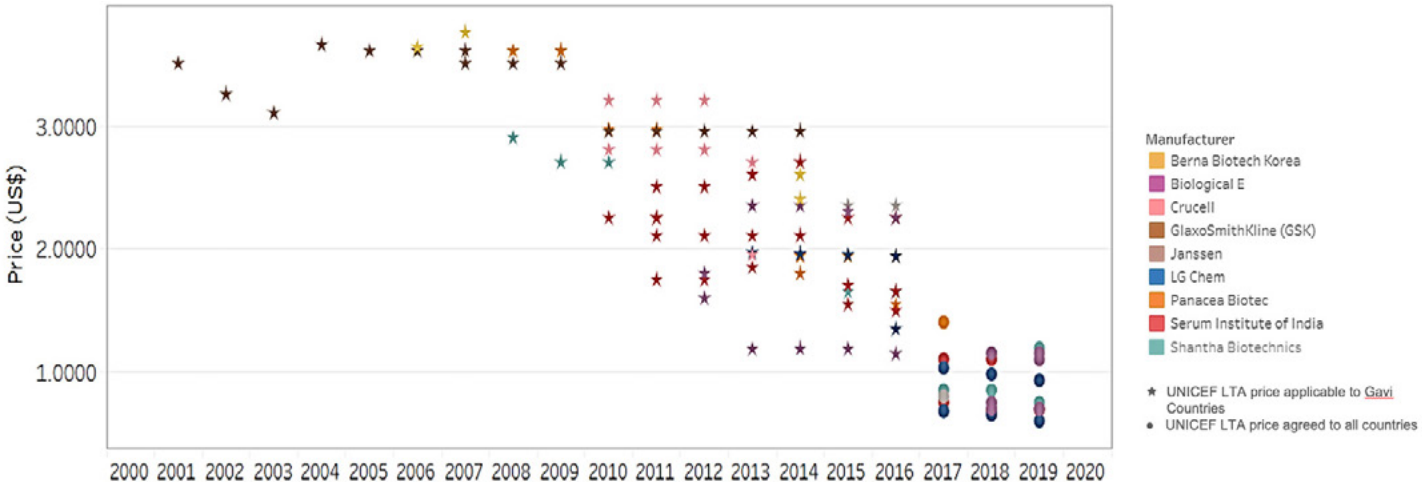
Pooled procurement is their primary tool. For example, UNICEF pools the vaccine orders of nearly 100 countries (UNICEF, 2019), and PAHO pools 41 countries (PAHO, n.d.). Other traditional procurement tools that these organizations use include multiyear contracts, demand forecasting, up-front payment bundling of products, and volume guarantees. This increases the bargaining power of LICs and MICs and gives vaccine manufacturers an incentive to supply these markets by leveraging economies of scale.

Pooled procurement has concentrated the buyer base, resulting in significant pricing pressures. Using volume as the primary mechanism, procurement agencies demand lower prices for vaccines than LICs and MICs could negotiate individually with vaccine manufacturers. In addition to pooled procurement, multinationals are subject to pricing pressures because the DCVMN gives procurement agencies a competitive alternative.

The use of the pooled procurement mechanism only for vaccines in LICs and MICs introduces the concept of a price tier for each market, which ultimately depends on country income level. An estimated 80 percent of vaccines procured through pooled mechanisms are priced below the prices available to countries that self-procure (WHO, 2018). At the same time, self-procuring HICs pay prices that average five times more than self-procuring MICs (see Figure 8) (WHO, 2018).

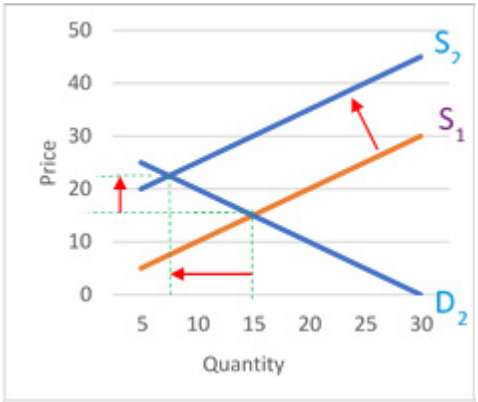
The strong emphasis on vaccine prices has made the LIC and MIC markets less viable for vaccine manufacturers. The singular focus on price has had some adverse consequences for the vaccine market. For example, through innovative procurement and funding mechanisms developed by UNICEF and Gavi, the price of the pentavalent vaccine being sold to LICs was reduced from $2.98 in 2010 to $0.79 in 2019 (see Figure 9) (UNICEF, 2019).

Figure 9. A race to the bottom- Prices in the penta market 2000-2020



Source: UNICEF, 2019.

Figure 10. Supply shift as manufactures exit the market



Source : KPMG Economic Services, 2020.

This price reduction has resulted in an outflux of profit-seeking vaccine manufacturers from the pentavalent market, leading to a reduced supply (see Figure 10).

Critically, this has also left insufficient margins for the remaining vaccine manufacturers to fund R&D once they pay their manufacturing costs. In addition, the extremely large sunk costs associated with vaccine production are not taken into account when manufacturers are being assessed for wider market interventions and assistance from donors and procurement agencies.

This story is expected to play out over and over in the coming years in other vaccine categories. Continued downward pricing pressure from international procurement organizations and the expectation that vaccines should cost "pennies per dose" will drive

large manufacturers from the LIC and MIC markets as they cease to be viable. ***The circular impact of lower prices and lower margins is a disincentive for vaccine R&D targeted at LIC and MIC markets***. The lower prices for vaccines mean manufacturers have very limited funds for R&D and will not invest them in a new vaccine that will also have low prices. The result is that the R&D funding bucket becomes depleted.

INTERNATIONAL FINANCING

Different funding and market strategies have been used by various international organizations to bolster vaccine development and access, while attempting to maintain a sustainable vaccine market. Examples of organizations operating in this space include the Bill & Melinda Gates Foundation, MedAccess, the Clinton Health Access Initiative and PATH. One of the recurring problems addressed by these organizations is the lack of incentives for vaccine manufacturers serving LICs and MICs to innovate. Some of the tools used by international organizations to encourage innovation are:

- **Funding R&D and volume guarantee**: Some organizations will provide no-cost or low-interest loans or grants to manufacturers to help facilitate and de-risk the R&D process in exchange for a pre-negotiated low-price vaccine. Often, the arrangement includes a volume guarantee from the funder to the manufacturer, for specific LIC markets. In return, the manufacturer agrees to a global access agreement for the intellectual property associated with the vaccine and often provides transparency into the full manufacturing costs. This tool effectively mitigates the risk of R&D failure for the manufacturer and provides a guaranteed volume level for the first few years of manufacturing, helping to break the circular impact of low prices and low margins.
- **Advance market commitments:** Under an advance market commitment, donors pledge to purchase a new vaccine for developing-country diseases (e.g., a malaria vaccine) at a price that would generate revenues that match other health products in a global competitive marketplace. The donors commit to paying a set price for a certain number of doses, after which the vaccine manufacturer is obligated to sell to eligible countries at an agreed-upon lower price that is affordable in the developing world.

  For donors, the commitment ensures that vaccines are available in the LICs and MICs that bear the biggest disease burden. This is also meant to stimulate competition among manufacturers to produce the vaccine as quickly as possible in order to claim

the guaranteed price (Zandonella, 2005). However, their use has had some perverse incentives in that they have driven vaccine prices to an extremely low level without providing any backstop for the lost margin needed by manufacturers for R&D investment.

- **Product development partnerships:** This tool allows different members of the vaccine market to come together to innovate and develop vaccines. Partners research, develop and facilitate access to new health technologies that target diseases that disproportionately affect populations in LICs and MICs. They effectively work as a risk-sharing agreement for the vaccine developer and accelerate vaccine development by bringing together the diverse strengths of stakeholders. There are currently 16 major product development partnerships operating globally (Product Development Partnerships, 2014).

Another tool is the Access to Vaccines Index, a nonfinancial incentive created for companies to encourage improved access to their vaccines, with their contributions recognized publicly in the index. Intended as a reporting tool, it also has a public relations function for manufacturers.

The Bill & Melinda Gates Foundation is a key Gavi partner in shaping the vaccine market and is a dominant figure in creating incentives for vaccine innovation. One example of its role is CEPI, mentioned above, which provides incentives to encourage the development of vaccines to prevent and respond to future epidemics and to secure equitable access for the populations who need them. CEPI was born out of the experiences of the Ebola epidemic in West Africa, which demonstrated the need for new global mechanisms to coordinate and fund health technology R&D to meet epidemic threats where market incentives fail.

THE IMPACT OF COVID-19

In many respects, the story of the COVID-19 vaccine development process is consistent with the overall state of the vaccine industry. Manufacturers are investing hundreds of millions

of dollars into developing a novel vaccine, with significant support from governments and public-private partnerships. However, the race to develop the COVID-19 vaccine has revealed some good, bad and ugly aspects of global economics and politics.

There has been unprecedented alignment between the priorities of vaccine manufacturers and public health. A key challenge in the vaccine market is that manufacturers are driven by profit potential and shareholder returns, while governments are driven by public health priorities, a prime dynamic for creative market-shaping activities. But the COVID-19 pandemic has flipped this situation on its head, with manufacturers and government aligned on the same goal at the same time.

- *The Economist* estimates that governments have invested upward of $10 billion in the development of a COVID-19 vaccine. While this investment is unprecedented, the number is less impressive when compared to the $7 trillion committed by governments around the world to manage the economic impact of the pandemic (The world is spending, 2020).
- Vaccine manufacturers have come together in an unprecedented manner. Just one example is an agreement between a group of six biopharmaceutical companies (Eli Lilly, AbCellera Biologics, Amgen, AstraZeneca, Genentech and GlaxoSmithKline) to exchange "technical information" on their respective manufacturing processes and platforms for COVID-19 monoclonal antibody treatments. To enable this information sharing, the U.S. Department of Justice had to issue a ruling that granted permission under antitrust laws to enable the exchange. This is a complete departure from business as usual for an industry that is famous for its secrecy (Black, 2020).
- Countries are demonstrating that they understand the need for cooperation. COVAX, a global initiative co-led by Gavi, CEPI and the WHO to accelerate the development and manufacture of COVID-19 vaccines, has the participation of 172 countries. COVAX has nine CEPI-supported vaccine candidates and nine more vaccines under evaluation. The alliance is in the process of securing funding from self-financing participants in order to secure enough doses of successful vaccines for the world's most vulnerable populations, including health care workers and the elderly (WHO, 2020c).

Governments are using all the tools at their disposal to limit the risk of vaccine manufacturers. Risk is a key driver of decision making by vaccine manufacturers. Volume guarantees, which limit the risks and enable them to reduce prices and ensure supply

security, are one of the tools that organizations such as the Bill & Melinda Gates Foundation and Gavi use (William Davidson Institute at the University of Michigan, 2015). These guarantees have been widely employed by governments during the COVID-19 pandemic, with preorders of 5.7 billion doses around the world from the five current vaccine candidates (excluding the Russian candidate). This includes pre-commitments from the United States for 700 million doses from five manufacturers, from Europe for 700 million doses from two manufacturers, from Japan for 490 million doses from three suppliers and from CEPI for 300 million doses from one manufacturer (Couronne, 2020).

Developing the vaccine is only part of the solution. Several factors complicate the ultimate objective: achieving global herd immunity. In addition to successfully developing COVID-19 vaccines, manufacturers will need to produce enough doses, pack them appropriately and get them to consumers. While manufacturers appear to be cooperating to ensure adequate manufacturing capacity, packaging is a different matter; medical glass has been in short supply since before the pandemic, and manufacturers seem to be competing to secure their own supplies. Similarly, logistics companies are struggling to keep up with demand for consumer products and medical gear and will have limited capacity for vaccine distribution (Chen, 2020).

Perhaps more alarming is the question of access to the vaccine, especially given the complex economics of the vaccine market. The same tools that maximize the possibility of a successful vaccine could lead to extreme disparities in who gets vaccinated. For example, by funding and preordering COVID-19 vaccines, HICs are taking steps to secure their own supplies but leaving out LICs and MICs that lack these resources (Chung, 2020). Despite the pooling of resources through initiatives like COVAX, many countries are taking matters into their own hands by signing their citizens up as volunteers for COVID-19 vaccine trials in a desperate attempt to ensure access. This is evident in the Philippines for Russia's vaccine candidate (Duterte volunteers, 2020) and in Bangladesh for China's Sinovac vaccine candidate (Paul, 2020).

COVID-19 could threaten decades of hard-won progress in the vaccine market. As governments and institutions around the world dedicate enormous amounts of money to finding a COVID-19 vaccine, multinational vaccine manufacturers and DCVMN companies are actively converting production capacity from other much-needed vaccines to ready themselves to manufacture the COVID-19 vaccine. The result remains to be seen. Will there be less funding and manufacturing capacity available for other vaccines that LICs also desperately need? How long will this disruption last? What will the resulting impact be on health and mortality?

At the same time, disruptions in delivery and uptake caused by the COVID-19 pandemic and the shutdowns in various countries have caused what the WHO and UNICEF have called "an alarming decline in the number of children receiving life-saving vaccines around the world." In the first four months of 2020, the coverage for the third dose of the DTP vaccine (DTP3) has declined for the first time in 28 years, and there are real concerns about resurgent measles outbreaks around the globe (WHO, 2020b).

CONCLUSION

To summarize the key points of this paper, the complex global vaccine market is characterized by multiple actors with very different goals, and multiple markets with different needs. Manufacturers, both multinational corporations and DCVMN companies, seek profits but do so in different ways, with the former looking to lower-volume, higher-margin markets and the latter looking to higher-volume, lower-margin markets.

Multinationals have large and diverse portfolios of products, while DCVMN companies have smaller portfolios. Countries shape the demand and are the end users of the vaccines, seeking to vaccinate as much of their populations as possible. LICs and MICs have limited resources with which to buy vaccines and seek low prices but have large populations. HICs are able to pay higher prices but have smaller populations. There are also the various international actors that shape the procurement policies and funding mechanisms using different market-shaping tools. (See Table 4 for a general summary of these characteristics.)

As noted above, all of this creates growing tension. Given the differing vaccine needs in LICs and MICs compared to HICs, the impact of lower prices and lower margins continues to have a negative impact on vaccine R&D for diseases that are prevalent in developing markets. How will R&D be funded if not by manufacturers?

Table 4. Summary of vaccine manufacturer characteristics

	COMPANY 1 MULTINATIONAL	COMPANY 2 START-UP	COMPANY 3 DCVNM	COMPANY 4 DCVNM
Location	HIC	HIC	MIC	LIC
Product Portfolio	30 drugs + 10 vaccines	4 drugs + 2 vaccines	4 drugs + 2 vaccines	2 vaccines
Market	HICs, MICs, LICs	HICs	MICs, LICs	MICs, LICs
Revenues	$30 billion	$0	$100 million	$10 million
Net Income	$7 billion	$0	$3 million	$0.3 million
R&D Expenses	$5 billion	$25 million	$12 million	$1.2 million
Source of R&D Funding	• Net income • Private investment • Direct and indirect government investment	• Private investment • Direct and indirect government investment	• Net income • Private-public partnership investment • Direct and indirect government investment	• Net income • Private-public partnership investment • Direct and indirect government investment
How to Incentivize R&D?	• Enable price maximization in HICs • Indirect government investment	• Enable price maximization in HICs • Enable private investment • Direct and indirect government investment	• Enable volume maximization • Enable private/ public partnership investment • Direct and indirect government investment	• Enable volume maximization • Enable private/ public partnership investment • Direct and indirect government investment
What Disincentivizes R&D?	Low R&D productivity	Access to funding	Access to funding	Access to funding
Who Can Impact These Incentives and Disincentives?	Demand / markets	Funders / demand / markets	Procurement strategies / funders	Procurement strategies / funders

Source: KPMG Canada.

COVID-19 has thrown a very interesting wrench into this system, highlighting the best and worst characteristics of the vaccine market and causing deep concern over the lasting impact of redirecting financial resources from other diseases. COVID-19 presents a truly global vaccine need, and the response reflects truly global vaccine development, but the very different abilities of countries to pay is also leading to a rise in "vaccine nationalism."

At its core, the vaccine market behaves like any other market — it responds to supply and demand. However, unlike other markets, the impact of market failure for vaccines can literally be a matter of life or death.

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THE R&D RESPONSE TO COVID-19: WHAT CAN WE LEARN FOR THE VACCINE ECOSYSTEM?

Anis Chagar, Michael Thomas, Linda Zuo and Mike Watson

INTRODUCTION: AN UNPRECEDENTED RESPONSE

The COVID-19 crisis has generated an unprecedented research and development (R&D) response across the life sciences sector. From a near standing start in February 2020, more than 700 projects are now under way, examining vaccines, antivirals and other treatments to manage and prevent the spread of the disease and treat severely affected patients (Biotechnology Innovation Organization, 2020).

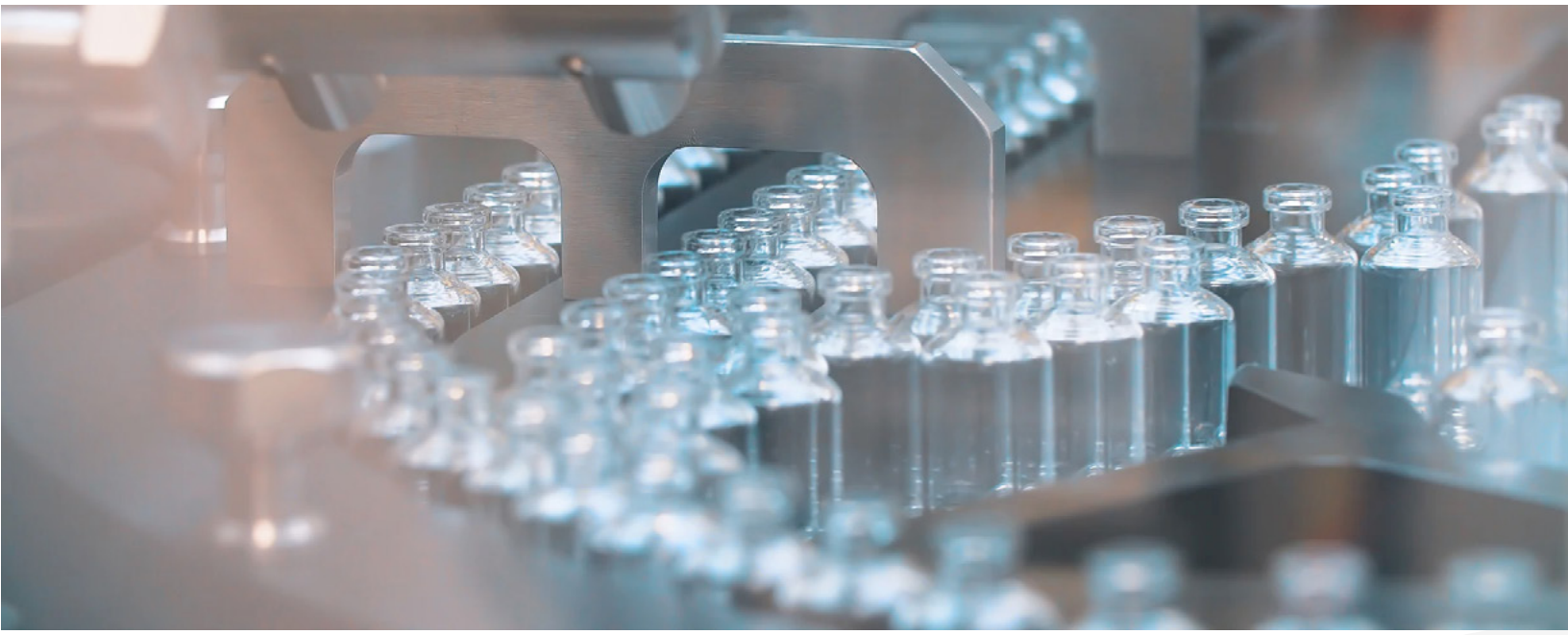
While some of these efforts have repurposed existing technologies, almost half represent novel R&D initiatives. Of the 170-plus vaccine projects listed by the World Health Organization (WHO), 95 percent involve totally new vaccines (the remainder have been repurposed).

The remarkable scale and speed of the response has been far beyond anything seen in previous pandemics. As of summer 2020, nine vaccine candidates are already in Phase 3 trials, with 25 more close behind, and the testing pipeline carries some 130-plus preclinical candidates (WHO, 2020). With so many shots at the target and the diversity of R&D platforms being explored, confidence is rising that we will see a successful vaccine by the end of 2020 or early 2021. Indeed, by then we may see multiple types of vaccines available to the global community to contain the catastrophic global impact of this pandemic.

A DEVELOPER'S PERSPECTIVE: LEARNING FROM COVID-19?

The Sabin-Aspen Vaccines Science & Policy Group commissioned research from global management consultancy Kearney to better understand the vaccine R&D response to the COVID-19 crisis, with a particular focus on organizations actively involved in developing vaccine candidates. The study looked at the makeup of the organizations driving the research effort; their motivations, ambitions and funding; and the unique challenges that they have encountered.

The objective is to understand whether this is a one-time response or whether it offers insights for effectively preparing for future pandemics and perhaps creating an R&D ecosystem better able to rapidly and effectively address the world's greatest health challenges. The research was conducted in July and August 2020, using surveys and interviews with companies and organizations involved in COVID-19 vaccine development as well as online research.



We approached more than 100 vaccine developers and received responses from 17 organizations. The survey respondents represent the diversity of the R&D effort around the globe and include a mixture of government-owned, private and publicly held entities. They include two companies that have clinical candidates; the remainder are testing products in a

preclinical phase. The typical respondent had been established for over 10 years, and all have been in operation for at least two years. All but one had experience in developing vaccines, and the great majority had previously marketed vaccines or conducted extensive research on them. The survey respondents provide a credible snapshot of small biotech and mid size firms, as well as insights from large, established vaccine players.

> The objective is to understand whether this is a one-time response or whether it offers insights for effectively preparing for future pandemics and perhaps creating an R&D ecosystem better able to rapidly and effectively address the world's greatest health challenges.

As with all COVID-19 research, the data reported in this paper can only be accurate at the time of writing. At this stage, findings can be considered "directional," and more extensive research will undoubtedly add to the knowledge base.

The majority of our research was based on the WHO-published vaccine pipeline as of July 24, 2020, supplemented by analysis from the Milken Institute. To ensure the most current picture possible, we also drew on WHO pipeline data as of September 9, 2020, to update some of the information; these updates are referenced in the citations.

The paper looks first at the composition of the research response effort: Who are the players, where do they come from, what technologies are they exploring and what has motivated them to get involved? We then explore how efforts are being resourced: What are the funding sources, what activities does the funding cover, what role do partnerships and collaboration play in the response effort and what are the challenges? The final section of the paper explores what can be learned from the current response effort, both during the immediate crisis and for future pandemic and health research efforts.

THE PLAYERS AND THE PLATFORMS

A BROAD R&D RESPONSE COVERS BOTH CONVENTIONAL AND NOVEL APPROACHES

The COVID-19 pipeline currently consists of 170-plus candidates at various stages of development and spread across different technologies and platforms (see Figure 1) (Kearney et al., 2020). Sixty-six percent of the pipeline consists of "conventional" technologies, mainly protein subunit vaccines (about one-third of all candidates), replicating viral vectors, and inactivated viruses. The remaining 34 percent of the candidates involve novel technology platforms, primarily based on RNA and DNA and nonreplicating viral vectors.

Figure 1. COVID-19 Vaccine platform overview

34% of the candidates are based on novel technology platforms that have not been commercialized before

	% of COVID candidates*	COVID vaccine latest progress: Pre	I	II	III	Platform attributes: License platform	Past examples	Speed	Current scale
new Protein subunit	33%					✓	– HPV, Pneumococcal Disease, Tetanus, Hep B, Meningitis	Med–Fast	High
new RNA-based	14%					✗	– nA (veterinary use only)	Fast	Low
Nonreplicating viral vector	12%					✗	– nA (veterinary use only)	Med	High
new Replicating viral vector	9%					✓	– Measles	Med	High
DNA-based	8%					✗	– nA (veterinary use only)	Fast	Med
Inactivated virus	6%					✓	– Hep A, Influenza, Polio, Rabies	Med	Med–High
Virus-like particle	6%					✓	– Hep B, HPV	Med–Fast	High
Live attenuated virus	2%					✓	– Measles, Smallpox, Chickenpox, Yellow Fever	Slow	High

Source: WHO, *New England Journal of Medicine*, Milken Institute, Kearney

* *Platform unknown = 11%*

Source: WHO; New England Journal of Medicine; Milken Institute; Kearney, 2020.

The hope that RNA- and DNA-based platforms can promote rapid development is borne out by the fact that 10 out of the 34 candidates in clinical development employ those platforms. The Chinese experience with inactivated virus approaches, however, shows that conventional technologies can also be used for rapid development (WHO, 2020).

The potential risks of investing in novel platforms with no prior track record has been debated, given questions both about efficacy and safety and about economic and scale-up viability (Van Riel & de Wit, 2020). Overall, however, the COVID-19 R&D response has created a balanced portfolio of research options, although they do not all attract the same level of funding, as discussed later.

HIGH-INCOME MARKETS DOMINATE RESEARCH EFFORTS, BUT ASIAN DEVELOPERS ARE WELL REPRESENTED

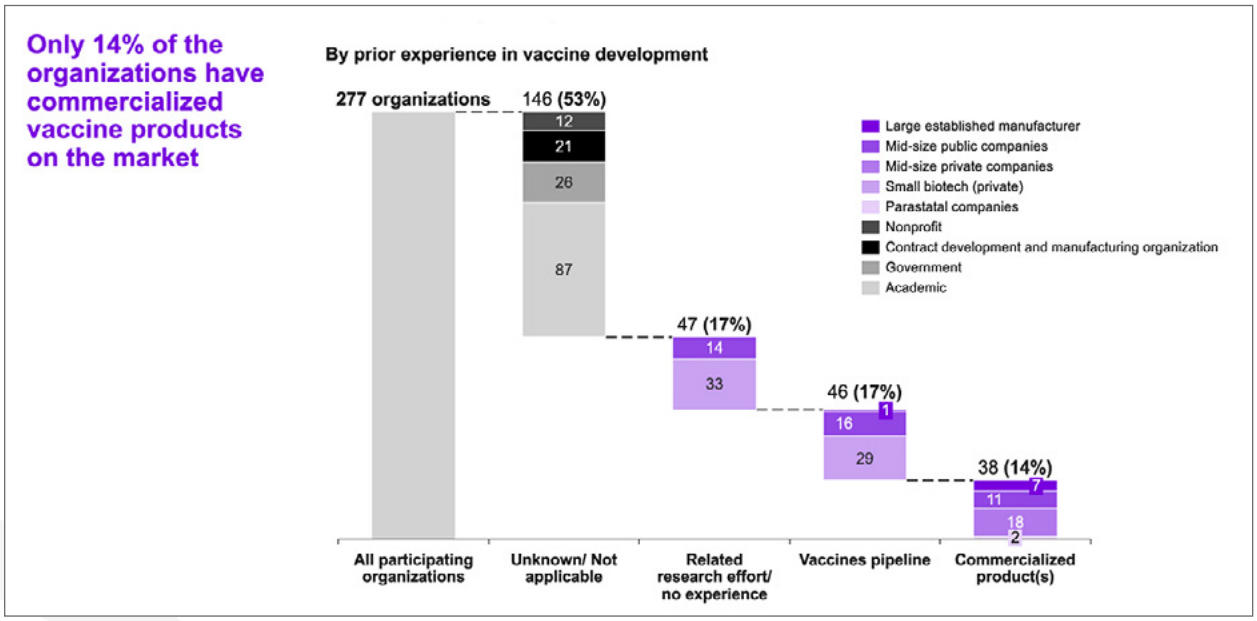
Although there is a concentration of research activity in high-income countries where the lead developers are based (accounting for 69 percent of candidates), the effort is truly global. Thirty percent of lead developers come from upper-middle-income countries, especially in

Asia, where China and India are dominant. Lower-middle-income countries are responsible for a dozen or so candidate projects through developers that include BioNet (Thailand) and the National Research Center (Egypt) (WHO, 2020). This mismatch between disease burden and research location is obviously a concern, especially given supply-chain scaling constraints and the perceived threat of vaccine nationalism.

PARTICIPATION ACROSS THE INNOVATION ECOSYSTEM, FROM EXPERTS TO NOVICES, MOTIVATIONS VARY

More than 270 organizations are involved in developing the 170-plus COVID-19 vaccine candidates registered on the WHO database (WHO, 2020), and our analysis shows that participation comes from across the innovation ecosystem (see Figure 2). The development landscape includes large, established manufacturers and vaccine players, as well as smaller biotechs, startups and academic institutes (the latter group collectively represents almost 60 percent of the organizations involved). Government agencies and parastatal companies (i.e., state-owned or state-directed companies) also play an important role, particularly in middle-income countries.

Figure 2. Individual player segmentation



Source: Kearney analysis, with data from WHO and Milken Institute trackers, July 24, 2020.

Perhaps surprisingly, experience does not appear to be a barrier to getting involved. Based on our analysis, only 14 percent of the organizations have commercialized vaccine products on the market; another 17 percent have a developed vaccine pipeline but have yet to bring a vaccine successfully to market. A further 17 percent have related experience with the technology involved (e.g., DNA and RNA) but no previous forays into vaccines. We have not found evidence of prior experience in vaccine development or directly relevant platforms for the remaining 53 percent of players, mostly academic institutions. It is worth noting that most of the 34 clinical candidates under development are driven by organizations with proven vaccine development or commercialization experience (WHO, 2020). The broader involvement that is driving a lot of the preclinical development effort could fuel future waves of innovation.

PRIOR VACCINES AND PANDEMIC EXPERIENCE ACCELERATE ENGAGEMENT

Our survey offers some insights into why organizations engage in the effort. Most of our respondents moved rapidly, with 80 percent having programs up and running by March. Indeed, several were already active in January, before a global pandemic was formally announced. A relatively smaller number joined the race later, between April and July 2020.

The reasons for getting involved varied greatly, but half the respondents had existing related research and platforms that could be easily repurposed. Early identification and publishing of the RNA sequence accelerated the response effort. COVID-19 prompted a totally de novo research initiative for only a small minority of respondents, typically motivated by the desire to rapidly build capability in new platforms. Strikingly, nearly all our respondents had responded to prior pandemics, reporting experience with Zika, Ebola, MERS, SARS, H1N1 or global influenza initiatives. Experience with a single type of platform did not seem to be a predeterminant for involvement. Most respondents had already developed their "pandemic response muscles" and were aware of the challenges and stakeholder environment, response timeline and required processes.

Commercial market potential was also a key consideration. Most of our respondents hope to see their projects through to commercialization. Advanced market commitments have played an important role in signaling future market demand and are increasingly providing pricing clarity.

Key reasons why some companies delayed their entry into the research, particularly emerging market developers, were the inability to access funding and lack of access to and familiarity with new technology platforms.

FUNDING THE COVID-19 RESPONSE

$10 BILLION IN HEALTH FUNDING COMMITMENTS MOBILIZED, FOCUSED ON FRONT-RUNNERS AND NOVEL APPROACHES

The COVID-19 pandemic response has mobilized considerable funding commitments. The three main funding blocs, which often overlap, are development funding and grants, co-investment in manufacturing infrastructure development and advanced market commitments.

Many of the headlines have focused on the multibillion-dollar commitments made by the U.S. government and its Biomedical Advanced Research and Development Authority (BARDA) since the earliest days of the pandemic. Total BARDA grants and advance commitments now exceed $10 billion (*The COVID-19 Health Funding Tracker*, 2020), with more than 85 percent of that going toward vaccine development and manufacturing (BARDA, 2020a). Significant additional funding vehicles include the Coalition for Epidemic Preparedness Innovations (CEPI), with current COVID-19 funding commitments of $1.2 billion (*The COVID-19 Health Funding Tracker*, 2020), and the Bill & Melinda Gates Foundation. As well, there are advanced market commitments from the European Union and individual governments, including the United States, Canada and the United Arab Emirates, and the COVAX initiative co-led by the WHO, Gavi and CEPI (Gavi, n.d.). In total, estimates suggest that more than $2.3 billion has been committed to the COVID-19 vaccine response through these channels, and that figure is rising (*The COVID-19 Health Funding Tracker*, 2020).

Development timelines and novelty have been primary criteria for BARDA and CEPI investment, so the primary beneficiaries of this investment have been the front-running candidates that use novel technologies (Cohen, 2020). While funding devoted to new technologies has no certainty of return, its availability does reflect interest in platforms that

might be applied in other pandemics, the promise for both COVID-19 and other research purposes, and a national interest in building excellence in new areas of science and manufacturing (BARDA, 2020b). Our survey response suggests that the same considerations apply to private equity investors. The funding ambition therefore goes well beyond COVID-19, potentially at the cost of backing a more balanced portfolio of candidates to respond to COVID-19 itself.

READILY AVAILABLE RESOURCES FOR EARLY DEVELOPMENT, EXTRA FUNDING REQUIRED FOR SCALING

A more mixed pattern of funding approaches emerges when we look beyond the front-runners to preclinical candidates and the next wave of innovation. Most of our respondents are funding current efforts with a mixture of external and internal funding, and several are fully internally funded; only a few depend solely on external funding.

Having existing funding in place and the ability to redeploy existing project resources most likely accelerated the COVID-19 response effort. Most of our respondents either already had projects in the area or, more commonly, were able to redeploy teams working on other projects toward the COVID-19 response at little incremental cost, at least for proof of concept and early development work.

Only a few of our respondents mobilized entirely new teams that required immediate net new expenditures. Most have funding commitments of less than $100 million, and the majority have less than $50 million, although the more advanced clinical projects have funding in excess of $500 million. For most of our respondents, current committed funding covers the proof-of-concept stage, up to smaller-scale Phase 1 and Phase 2 clinical trials. Only in a minority of cases could existing funding extend to financing Phase 3 pivotal trials. Existing funds also seem to cover manufacturing scaling and technology transfer in 60 percent of cases. All told, half of our respondents appear to be fully or nearly fully funded, while the rest will require additional funding, at a level that matches their existing funding commitments, to complete development and manufacturing scale-up.

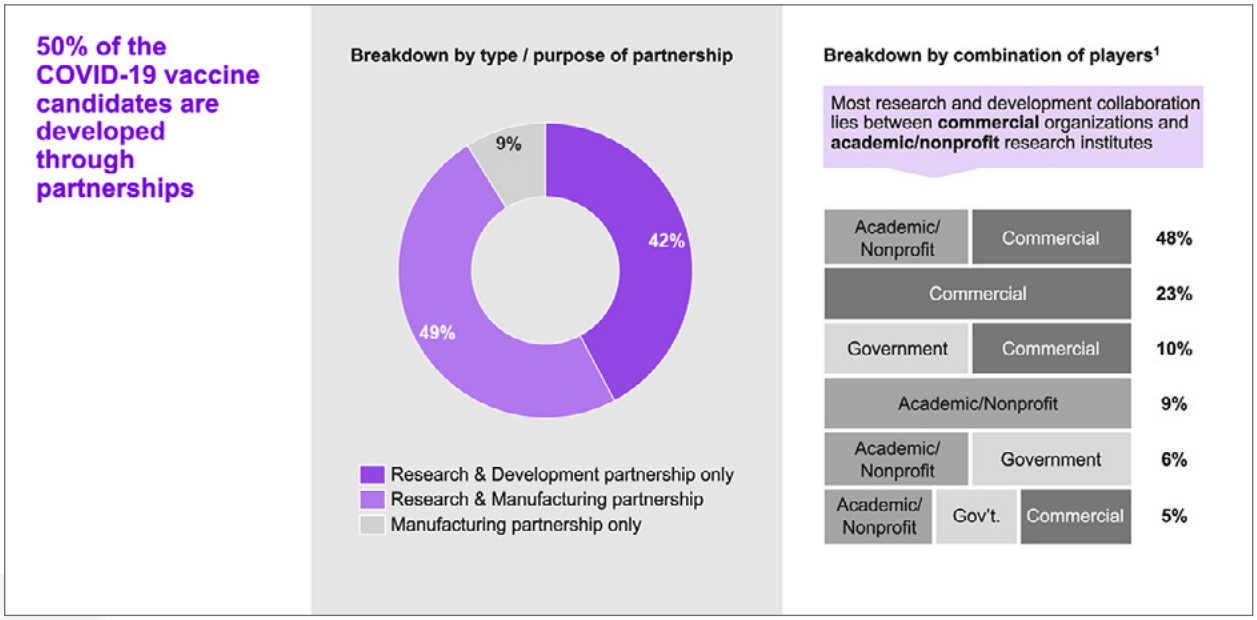
THE ROLE OF PARTNERING IN THE RESPONSE

Partnering is a significant feature of the vaccine R&D COVID-19 response, with an average of 1.5 organizations involved in each project. Our respondents generally report a higher level of collaboration than is typical for similar programs, and the speed at which teaming has evolved and the central role that academic institutions play in developing the science are striking features.

HALF THE VACCINE CANDIDATES DEVELOPED IN PARTNERSHIP, WITH ACADEMIC INSTITUTIONS THE MAIN SCIENTIFIC PARTNER

Our analysis indicates that about half the COVID-19 vaccine candidates involve some form of development, manufacturing or commercialization partnership, including most of the 34 clinical candidates (see Figure 3) (WHO, 2020). This reveals that both solus and collaborative research approaches are being used equally across the continuum of the COVID-19 response.

Figure 3. Segmentation of partnership



Source: Kearney analysis with data from WHO and Milken Institute trackers, July 24, 2020.

Of the 90 development candidates currently in partnership, 63 percent involve two partners while 21 percent involve three partners, and the balance have four or more, including the Oxford University and AstraZeneca candidate, which has an extensive network of local manufacturing agreements.

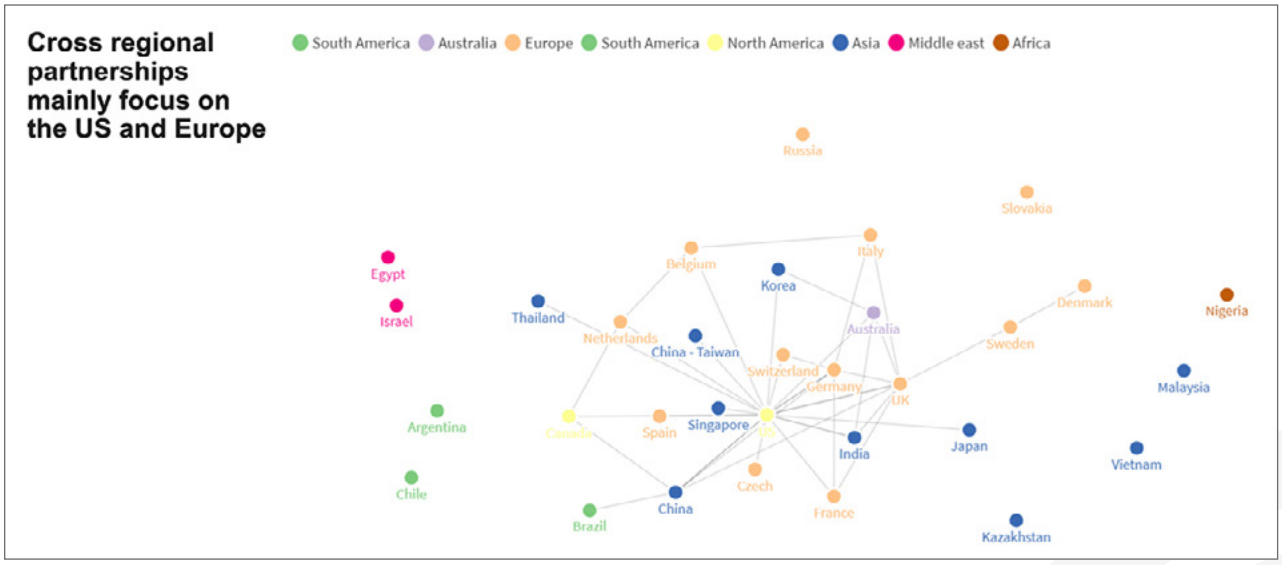
Partnerships principally fall into two categories. R&D partnerships between two research entities account for almost half of all the partnering activities; research and manufacturing partnerships that involve a research entity and a clinical development, manufacturing and commercialization player account for just over 40 percent.

The most common partnering combination is between an academic or not-for-profit research entity and a development, manufacturing and commercialization partner, which account for just under half of all partnering models. Partnerships between two commercial players account for 23 percent of partnerships.

MANY PARTNERSHIPS CROSS BORDERS, MAINLY BETWEEN THE UNITED STATES AND EUROPE OR WITHIN EUROPE

Cross-regional partnerships account for almost 40 percent of all partnerships. International teaming involving a U.S. player is the key model, accounting for 79 percent of these cross-regional partnerships. Intraregional partnerships, primarily in Europe, account for 17 percent of partnerships. Developers at the "periphery," such as Egypt, Israel, Argentina, Chile, Russia, Nigeria, Malaysia and Vietnam, seem to be significantly less well-connected and do not appear to be partnering beyond their borders at this stage (see Figure 4).

Figure 4. Cross-country partnerships overview



Source: Kearney analysis, 2020.

PARTNERSHIPS ARE DRIVEN BY THE NEED TO ACCESS CAPABILITY, SHARE RISK AND ACHIEVE SCALE

Our survey respondents are considering additional partnerships both for research and for manufacturing and commercialization purposes. Research partnering is focused on accessing core science, delivery systems and technologies. As already noted, most respondents are committed to seeing their projects through to commercialization, intend to market the product themselves or in partnership, and report having sufficient manufacturing capabilities to scale in response to demand. Their reasons for partnering are to achieve further manufacturing scale and geographical reach and to de-risk the commercialization effort, with many recognizing that there is more than enough potential demand to be shared among partners.

SIX MONTHS INTO THE PANDEMIC: WHAT WORKS, WHAT DOES NOT

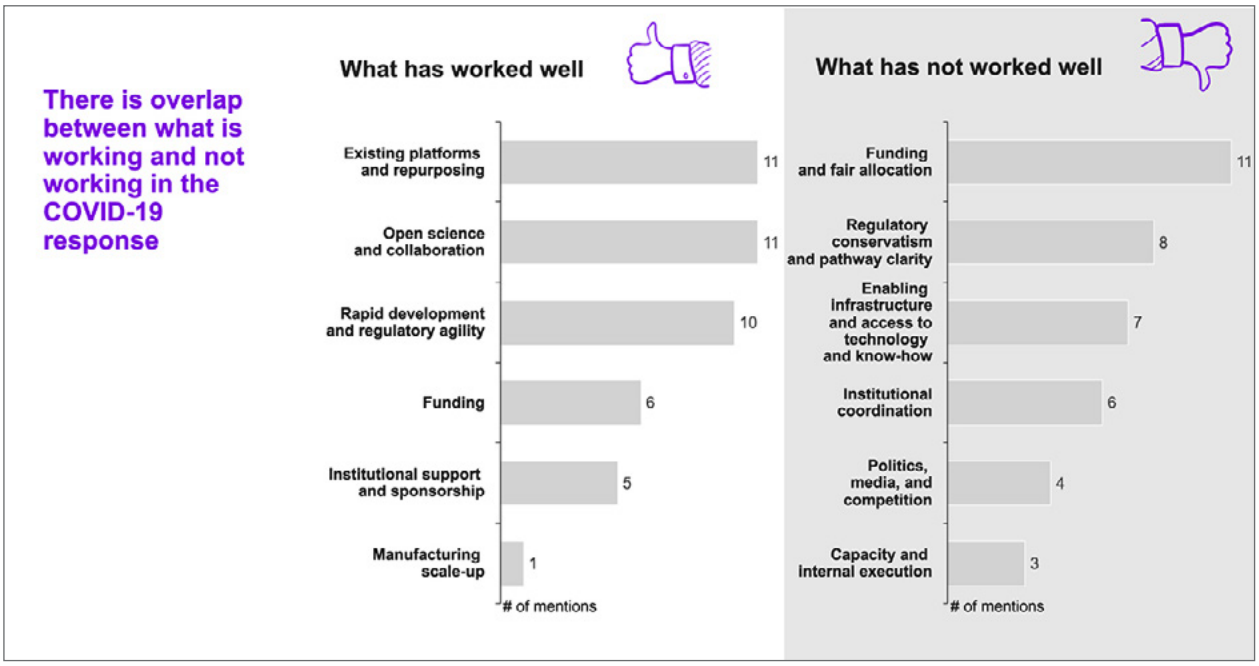
The COVID-19 vaccine R&D response has been moving extremely rapidly, mobilizing considerable scientific and financial resources and rapidly developing new institutional mechanisms. An impressive pipeline has been created at unprecedented speed, with the hopes of the world pinned on its success. The overall message from our respondents is that the early response has worked well, even if the institutional mechanisms have not always been transparent (see Figure 5).

But concerns remain about the next phase of the response and the legacy of a larger Western-driven scientific endeavor, especially as it pertains to global equity and resources to scale. This is very much the time to take stock, both to inform the current pandemic response and to strengthen future responses.

A number of key themes emerge from survey findings:

- Scientific preparedness and collaboration
- Regulatory clarity and agility
- Funding availability and access
- Institutional coordination and transparency

Figure 5. What has worked well and what has not



Source: Kearney Survey in partnership with the Sabin-Aspen Vaccine Science and Policy Group, 2020.

SCIENTIFIC PREPAREDNESS AND COLLABORATION

Availability of project resources, platforms and early collaboration enabled a rapid jump-start. All our respondents highlighted the speed and effectiveness of the initial development response. From the early dissemination of the RNA sequence of the virus to the rapid and effective sharing of scientific results, including prepublication results, the response was characterized by a high level of rapid information sharing, openness and transparency. The many players involved in the effort further amplified collaboration opportunities. As well, the availability of relevant platform technologies and capabilities, combined with an institutional openness to consider novel approaches (such as DNA and RNA platforms), helped to speed up early development activities.

The prior commitment of the WHO, CEPI and other global funders to related fields of research created a body of know-how that promotes confidence about moving rapidly in the early stages of the pandemic response. However, respondents also

commented on the lack of global scientific policy on research priorities and the absence of a "pandemic research readiness" response plan. That absence allowed funders to drive priorities perceived to be biased toward rapid, novel platform technologies rather than conventional approaches. A centralized view of the target technologies both for the immediate and potentially longer-term response would have been helpful, especially one that considered the appropriate role and balance between conventional and novel technologies and opportunities to mobilize development efforts beyond the most obvious markets.

In practical terms, the speed of the response was driven by the fact that companies had resources already devoted to research that could be rapidly redirected to COVID-19 in light of the public health imperative and commercial potential.

Respondents highlighted several development bottlenecks, however. Among them were limits to the testing infrastructure (e.g., laboratory analysis and assays), supply chain disruption of critical materials such as reagents and competition for the resources of clinical research organizations (CROs). A key learning opportunity is the importance of having a ready development infrastructure.

Looking forward, respondents expressed some concern about the continued open sharing of information, particularly as some candidates enter pivotal trial phases and move nearer to market. Similarly, information on new strains has reportedly not been as prompt as it was at the outset of the pandemic.

REGULATORY CLARITY AND AGILITY

Rapid regulatory engagement and openness to agile methods, but more end-game clarity needed. Along with openness, collaboration and the ready availability of resources and science to fast-track programs, early regulatory engagement was critical to the speed and quality of the initial response, particularly to accelerate preclinical development. Regulators were accessible, engaged and flexible about embracing new concepts, particularly for early-stage development candidates, and they have supported accelerated and dynamic clinical trial designs. Expedited reviews have ensured rapid progress at key decision points.

As projects move to more advanced stages of development, our respondents share a number of concerns about the clarity of the regulatory process. There is a perception that the key regulatory authorities (mainly the Food and Drug Administration) remain conservative,

particularly in relation to novel compounds as they move beyond proof of concept into large-scale trials. Equally, there are concerns that political interference could compromise safety standards.

Also worrisome is the limited guidance on the target product profile and technology platform and the perceived lack of clarity on the primary clinical endpoints necessary to demonstrate efficacy. There continues to be ambiguity about the regulatory route to market and the approval requirements both for emergency use and mass immunization. The challenge is even greater outside the major regulatory jurisdictions.

Coordination of global clinical trials also remains a critical issue, particularly at the scale of the clinical trials needed to access high-incidence populations and the likelihood that the branching of different COVID-19 strains will require an assessment of relative efficacy in different populations and cohorts.

FUNDING AVAILABILITY AND ACCESS

Major funding flows mobilized, but allocation not transparent or evenly spread. Survey respondents recognize the sea change in the adequacy of funding to support the COVID-19 vaccine R&D response, a rarity for some developers. However, funding remained a key concern for ultimate program success, especially as related to biases in how resources are allocated, both in terms of geography and technology.

Most of the mobilized funding has been in the United States, and to a lesser extent Europe, and national programs in China and Russia. In many instances, national policies and priorities are perceived to be dictating the direction of the scientific development. There is a well-founded perception that a considerable share of the funding has gone into novel (e.g., DNA and RNA) or strategic technologies, rather than conventional technologies, with an eye to speed and scientific innovation beyond the COVID-19 response. Respondents highlight the risk that the current funding approach may create a new vaccine oligopoly consisting of the early winners of the COVID-19 vaccine race.

Decision making has not always been transparent, and limited justification has been provided when developers have had their applications rejected.

Looking toward the next phase of the response effort, access to funding and resources remains the main concern. Given that only a minority of our respondents are fully funded for development and scale-up, most would need to raise capital at least comparable to what they had previously raised to complete their programs. Working capital to fund Phase 3 scale-up clinical trials is a particular concern. Some of the primary funders, including BARDA, CEPI and academic grantors, typically do not provide cash funding for the later clinical development phases and only selectively to build manufacturing capacity. In the absence of institutional funding, our respondents are looking for commercial partnerships to share the risk. A key concern for several developers is the continued availability and willingness to provide funding after one or several vaccines are approved. There is a perception that funding will rapidly contract and that many projects will be unable to progress beyond proof of concept or early clinical development.

INSTITUTIONAL COORDINATION AND TRANSPARENCY

While multilaterals prepared the ground, national governments have been the game changer. Beyond the immediate context of regulatory engagement and funding, institutional coordination was not a primary factor for survey respondents. After the early preparatory work by the WHO and CEPI, the real impetus for the response was the recognition by national governments of the urgency and scale of the issue. The role of the U.S. government has drawn attention away from COVAX as the sole response platform, and there are analogous approaches by other national governments to create and power the existing pipeline. Despite all the issues of transparent decision making and the risks of political interference, Operation Warp Speed in the United States is perceived as a game changer, providing focus and prioritizing resources on a narrower portfolio of potential winners.

One of the shortcomings of a government-driven response is that it inevitably fragments the quality of the global effort. Our survey respondents highlighted shortcomings at different

levels, from the absence of a coordinated and balanced vaccine research strategy to inform development efforts through the limited availability of research funding outside the major advanced centers.

Looking forward, the infrastructure for global trials and recruitment is perceived to need more coordination, as does the process for regulatory approval outside major established jurisdictions. These are immediate opportunities for action.

THE COVID-19 VACCINE R&D RESPONSE AND THE FUTURE OF VACCINE DEVELOPMENT

THE BAR FOR A QUICK RESPONSE TO A PANDEMIC HAS BEEN RAISED, BUT TRUST IS AT STAKE

The COVID-19 vaccine R&D response is recognized by our respondents as having a lasting impact on how vaccine development occurs in the future:

- The **demonstrated speed** at which products have been developed will change expectations of how quickly researchers and industry can respond
- The **agile regulatory response** and openness to in-line decision making and dynamic clinical trial designs have accelerated the time to market and taken years out of the development cycle
- COVID-19 has raised **global institutional and public awareness** of the essential role that vaccines continue to play in the public health response, unlocking exceptional funding
- If the current pipeline of candidates is successful, it will **validate platform technologies and especially DNA, RNA and viral-vectored technologies** as being able to provide a rapid response and amplify financial support for ongoing vaccine research in this area

The COVID-19 vaccine challenge has shown developers the potential speed and agility of the development process. For vaccine developers outside developed markets, it has also highlighted the important role of wealthier nations in any major pandemic response from scientific, policy and funding perspectives. Several respondents from middle-income markets mentioned the need to strengthen academic and commercial ties, especially with the United States but also with Europe.

However, the current response has been highly skewed toward large investments in unproven technologies, and our respondents shared concerns about political interference,

transparency of decision making, independence of the regulator, and fairness and equity in the distribution of resources. If these programs succeed, it will redraw the vaccine landscape to the detriment of other, perhaps more conventional approaches, which are the mainstay of many middle-income and emerging-market vaccine players.

Finally and importantly, the trusted relationship with the public is finely balanced, and the combination of a growing anti-vaccination movement, the association of speed with risk, and the potential for inequity in how an eventual vaccine is distributed and priced could, if not carefully managed, ultimately work against the global vaccine agenda.

CONCLUSIONS AND RECOMMENDATIONS

The COVID-19 vaccine response has mobilized resources on a scale and timeline that have never been seen in the context of a public health crisis. Recent experience with pandemics and, particularly, investment in platform technologies have strengthened the response muscle, supported by regulators and other governmental institutions that recognized the importance of immediate and agile decision making.

The scale and impact of COVID-19, the rapid global spread of the pathogen, the number of deaths worldwide and the huge economic costs and disruption of lockdowns have made curbing the pandemic an imperative. We are operating in an environment in which governments will do whatever it takes, with money no object. Companies, academic institutions and individuals have been highly motivated to redirect and repurpose existing efforts to respond to the pandemic.

While the unprecedented combination of factors that drove the COVID-19 response may not soon be repeated, lessons can be learned and embedded into the pandemic, epidemic and endemic vaccine response playbook. We propose the following recommendations for consideration:

- **Research strategy:** Several of our respondents highlight the fact that while most countries have a pandemic readiness plan, these plans do not contain a strategy for managing the therapeutic and immunization research response. This is seen as a critical gap. There is a need for a clear research response readiness strategy and also for securing very early (pre-pandemic) research advice to jump-start collaboration. Many researchers began their development before COVID-19 was officially declared a pandemic, even prior to its known spread outside of China.

- **Regulatory agility, coordination and end-game clarity:** The current response has shown how regulatory timelines can be dramatically accelerated and how developers can match their pace. However, early definitions of clinical endpoints and the target product profile/ technology platform are needed to provide clarity and transparency on the full route to market for developers. Greater global regulatory coordination is also required to align decision making outside the major jurisdictions. Rather than revert to previous timelines and attitudes toward risk, there is an opportunity to institutionalize the regulatory approaches developed for the COVID-19 response — particularly the demonstrated speed, agility and openness — for future pandemic, endemic and epidemic vaccine development. This could dramatically reduce the barrier to entry for future vaccines, improving innovation, choice and competition.

- **Warp speed for the world:** Multiple attempts have been made to create global funding platforms for pandemic response, including the establishment of CEPI. However, the involvement of national institutions has been a game changer. Our survey indicates funding requirements in the realm of $100 million to $200 million for early development up to scaling and in excess of $500 million for full scaling, pivotal trials and manufacturing build-out. A pipeline of 20 or more potential candidates or shots on target (as we currently have for COVID-19) would require a funding platform of $5 billion to $10 billion or more and rigorous selection of winners.

  COVAX is designed to provide exactly that, and it will be critical to identify successes and setbacks with CEPI, COVAX, Operation Warp Speed and other national approaches to inform future pandemic responses. Specifically, we need to know whether multiple financing vehicles are beneficial and create more options or dissipate effort. At a minimum, a pump-primed, ready-in-waiting global platform will benefit future responses. In principle, the same warp-speed philosophy could also be applied to

mobilize focused research to address other challenges, such as epidemic and endemic diseases, possibly with annualized R&D campaigns and funding efforts.

- **Balanced technology portfolio:** COVID-19 is a testing ground for platform and DNA and RNA technologies. However, the pipeline has clearly shown that other candidates are equally amenable to rapid development. The appropriate balance of novel and conventional technologies needs to be considered, as does facilitating the opening of platforms to ensure broader and more immediate access to developers around the world. Thought also needs to be given to the extent to which institutional funding obligations for pandemic responses should be accompanied by some commitment to intellectual property sharing, without comprising the attractions of participating as a developer.
- **Accelerating partnering platforms:** Collaboration and partnering have been defining features of the COVID-19 vaccine research response. Maintaining a state of readiness and bringing better visibility to the potential network of collaborators could allow development initiatives to start more quickly. This could be accomplished not only by matching academic institutions with commercial scaling partners but also by helping regional and national developers tap into the broader community. CROs, contract manufacturing organizations, testing providers and complementary technology providers (e.g., adjuvants) should be considered part of this collaboration ecosystem.
- **Funding continuity:** There needs to be clear continuity of funding available for proof of concept, early development and scale-up. Current funding vehicles have different remits requiring hand-offs throughout the development life cycle. This may be appropriate for routine research but not for accelerated pandemic research responses.
- **Global trial infrastructure:** A ready-made global network of distributed clinical trial centers is required for major epidemics to ensure that efficacy can be properly assessed in the context of different viral mutations and variations in case demographics.
- **A research trust bank for the future:** Much of the innovation and many of the preclinical candidates will not evolve into successful vaccines for COVID-19. However, many of them could be important accelerators and springboards for future coronaviruses and pandemics. We owe it to future developers to consolidate this rich substrate of innovation and make it as accessible as possible.

We are on the brink of a 12-month vaccine response, and the recommendations here could compress timelines further, perhaps to six or nine months, if everything is aligned from the start. In the context of COVID-19, this might have forestalled the spread to large parts of the world, including Brazil and India, and prevented the second wave of infections, saving

hundreds of thousands of lives and restoring economic health within a few months after lockdowns were largely enforced.

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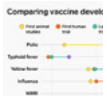

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