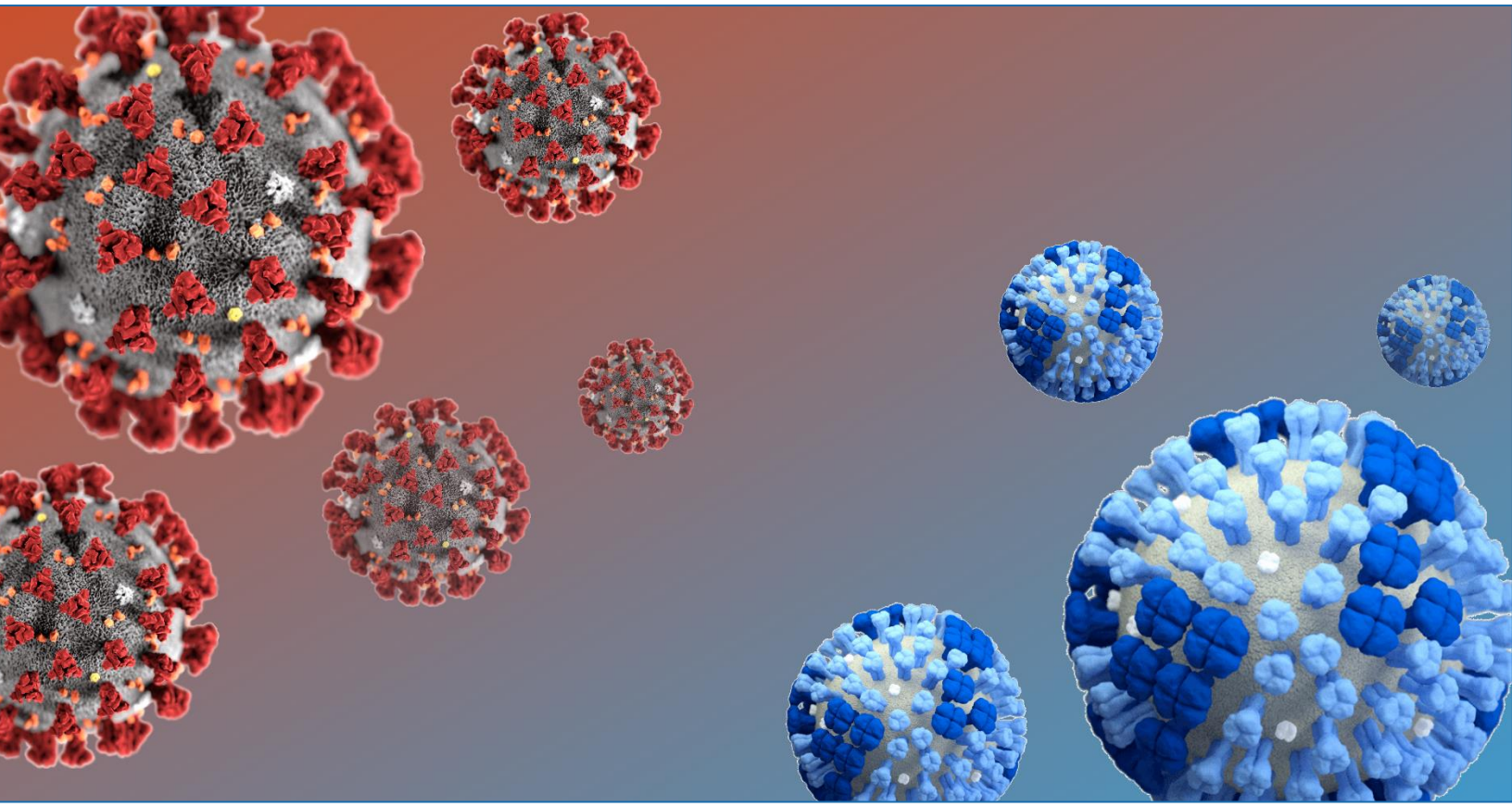

# LESSONS FROM COVID-19

## Advancing Development of Universal Influenza Vaccines

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## INTRODUCTION

For the past century, the modern pandemic experience was defined in large part by the global phenomenon of H1N1 influenza in 1918-20 (1)—a model now rapidly being revised, as COVID-19 spreads unchecked across an interconnected world. Despite decades of warnings of the threat posed by emerging infectious diseases (2–4), humanity has proven tragically underprepared to defend itself against a novel pathogen. As we suffer the consequences of this collective failure of unheeded foresight and imagination, we must seek knowledge that will prepare us to better face future pandemic threats—including the certain emergence of a novel influenza virus (5).

## RECKONING WITH COVID-19

Identifying and assessing the wide-ranging impacts of COVID-19 on diverse individuals, communities, populations, economic sectors, and systems will require years of scrutiny. Currently available measures of disease burden and socioeconomic disruption paint a grim picture that darkens with each day of uncontrolled disease transmission. At the time of this writing, approximately one year since the emergence of SARS-CoV-2 (the virus that causes COVID-19), the World Health Organization (WHO) reports more than 65 million confirmed cases of COVID-19, and 1.5 million deaths (6). Within the United States, the Centers for Disease Control and Prevention (CDC) reports more than 14 million cases and over 280,000 deaths since January 21, 2020 (7), and forecasts that nearly 330,000 COVID-19 deaths could be reported by the end of the calendar year (8).

These numbers vastly underestimate the health burden associated with COVID-19, as indicated by significant excess deaths during 2020 as compared with recent years (9). A combination of an overloaded health systems, along with fear of coronavirus exposure and barriers to care posed by social distancing measures, appear to have reduced uptake of preventive medical care, childhood immunizations (10,11), and diagnosis and treatment of life-threatening conditions, including symptoms of heart attack and stroke (12). The pandemic has also sparked a global mental health crisis (13), as rising rates of anxiety, depression, and suicidal ideation were met with disrupted mental health services (14,15).

In October 2020, the International Monetary Fund (IMF) estimated that lost productivity due to COVID-19 would cost the world $28 trillion through the end of 2025, of which $11 trillion would be lost by the end of 2021 (16). Using different methods, cumulative financial costs of the pandemic in the United States alone have been estimated at more than $16 trillion, or about half the nation's annual gross domestic product (17). However, as Nobel Prize-winning economist Joseph Stiglitz points out, "COVID-19 has not been an equal opportunity virus: it goes after people in poor health and those whose daily lives expose them to greater contact with others. And this means it goes disproportionately after the poor, especially in poor countries and in advanced economies like the United States where access to health care is not guaranteed (18)." Predictably, inequalities exposed and exacerbated by the coronavirus pandemic have sparked social unrest (19).

Policy and behavioral responses to COVID-19 have varied widely across the globe and over the course of the pandemic, from the level of national law (20) down to individual perceptions and actions (21,22). "Building the plane while flying it" has become the *cliché du jour*, as society responds to rapidly evolving epidemiological knowledge of SARS-CoV-2 and its myriad social implications.

The rapid and collaborative response by the scientific and medical communities to COVID-19 will surely rank among the most important and effective, and one that is potentially transformative (23–26). Academia, companies of all sizes, philanthropies, governments, and multilateral organizations have joined forces in cooperative enterprises unprecedented in both number and design to confront the pandemic threat (27–32). Information and results—including negative ones—are being shared beyond constraints previously imposed by intellectual property rights and competition for academic or market advancement. Pre-print servers medRxiv and bioRxiv have been flooded with coronavirus research outputs, albeit of varied quality(33), awaiting peer-review; scientific journals are being pressed to provide free access to their contents (34).

The phenomenal scientific response to COVID-19 has already produced a wealth of advancements, including diagnostic methodologies, treatment protocols, therapeutics such as monoclonal antibodies, and hundreds of vaccine candidates representing a range of longstanding and novel technologies. Promising vaccines, developed and tested in record time, not only inspire hope that this pandemic can be extinguished, but that productive changes forced upon the vaccine research and development ecosystem by COVID-19 can be sustained and applied to developing vaccines to avert future pandemics—and in particular, to tackle the persistent health burden and certain pandemic threat of influenza.

## DISARMING A LOOMING PANDEMIC

Devastating as the COVID-19 pandemic has been, and is projected to be, its death toll—now estimated at 1.5 million(6)—is dwarfed by that of the 1918-1920 influenza pandemic, which killed an estimated 50 million people (35). Subsequent flu pandemics in 1957,1968, 1977, and 2009 took between 2 and 4.5 million lives, combined. An influenza virus as deadly as the 1918 strain, which reduced the world's population by about 3 percent, would today cause more than 230 million deaths. "A worldwide influenza pandemic is literally the worst-case scenario in public health — yet far from an unthinkable occurrence," warned epidemiologist Michael Osterholm in 2018. "Unless we make changes, the question is not if but when it will come (36)."

Meanwhile, every year, seasonal flu costs 300,000 to 600,000 lives and millions of dollars in lost productivity—despite the existence of influenza vaccines that, while lifesaving, are far from ideal. To keep up with fast-mutating influenza viruses, flu vaccines are reformulated every year, and are rarely more than 50 percent effective at preventing infection. This is perhaps not surprising, since the annual vaccine is developed through a laborious process of tracking and predicting which viral strains will prevail. Moreover, more than 90 percent of flu vaccine is produced by egg-based manufacturing, which takes months to complete—during which time a novel influenza strain could easily spread across the globe, killing millions of people (37).

As the COVID-19 experience demonstrates, time is of the essence in the early stages of a pandemic. Even a heroic vaccine development effort takes months to bear fruit, while lives and livelihoods are destroyed.

Comprehensive protection from influenza necessitates a transition from reactive annual influenza vaccine development to universal influenza vaccines (UIVs): vaccines that provide lifelong or multi-year protection against a broad spectrum of influenza strains (38). Such vaccines would reduce barriers to access in many low- and middle-income countries that currently lack influenza immunization programs due to the expense and logistical difficulties associated with annual vaccination targeting most of the population. Most importantly, provision of UIVs before the emergence a novel influenza virus would provide the preemptive protection needed to prevent a pandemic before it starts. As the COVID-19 experience demonstrates, time is of the essence in the early stages of a pandemic. Even a heroic vaccine development effort takes months to bear fruit, while lives and livelihoods are destroyed.

Accelerating next-generation influenza vaccine research and development in pursuit of a UIV is the mission of the Influenzer Initiative at the Sabin Vaccine Institute. But, like the rest of the world, COVID-19 swiftly altered our efforts and our perspective. Recognizing that the vaccine R&D ecosystem was undergoing rapid and wide-ranging change in response to the pandemic, we committed to examine this transformation and its influence on the future of UIV development and the development of other vaccines against pathogens with pandemic potential.

## LEARNING FROM THE COVID-19 EXPERIENCE

The diverse, multi-sectoral community now responding to COVID-19—which includes many participants in influenza R&D—is gaining knowledge, tools and experience that that can be applied to advance progress toward a UIV. To learn how to sustain and harness this extraordinary momentum, we embarked on a multi-pronged investigation with three main goals:

- Capture novel and optimized approaches to vaccine development employed in this crisis;
- Identify factors that enable progress toward successful vaccine development, as well as persistent barriers to progress; and,
- Assess the potential impact of COVID-era advances on prospects for a UIV

To shape our inquiry and provide background and context for our findings, we are engaged in ongoing landscaping and analysis of relevant scientific literature, policy research resources, and public reporting. In October 2020, we anonymously surveyed a broad spectrum of professionals—in the life sciences, vaccinology, pandemic preparedness, vaccine regulation, policy, and funding—to capture quantitative and qualitative information. Survey questions explored three areas: vaccine R&D; drivers and incentives for COVID-19 vaccine R&D; and novel science and technology (S&T). We are also conducting interviews with key stakeholders in vaccine development to further examine the intersection of the R&D response to COVID-19, the threat of pandemic influenza, and the pursuit of a UIV.

Here we share our findings to date, including results from our survey, which received 235 responses from a diverse field of organizations (see **Figure 1**). Responses came from 46 countries, and eighty-two percent of the respondents identified as belonging to organizations currently involved in responding to COVID-19 (see **Figure 2**).

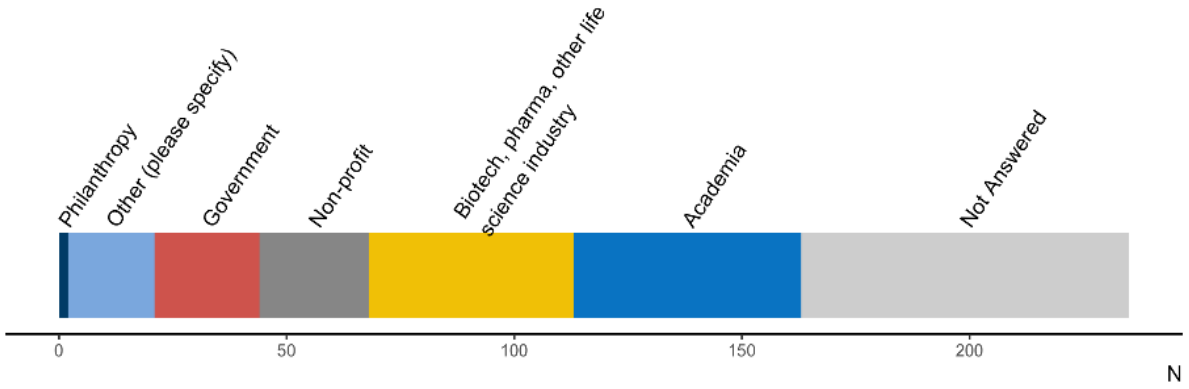



*Figure 1.Sectoral distribution of survey respondents.*

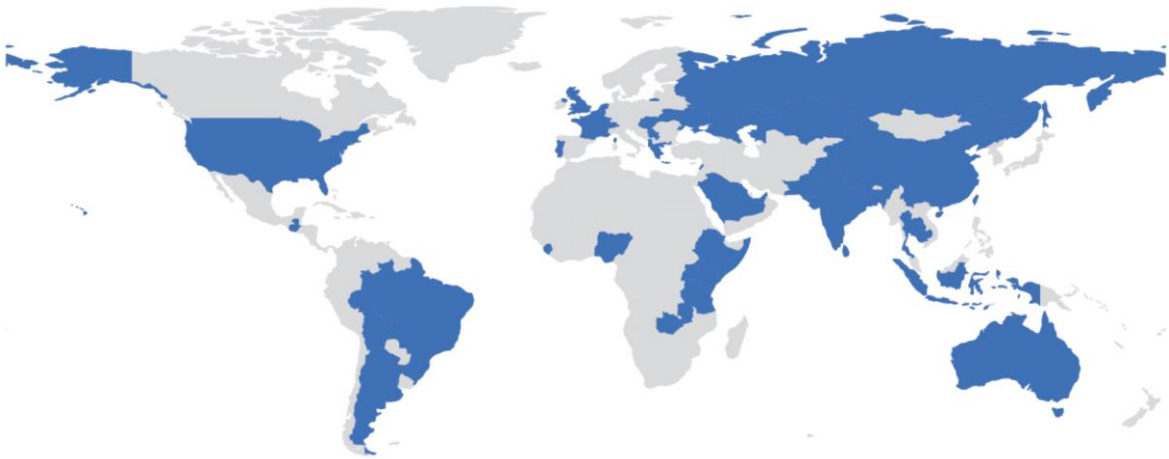


*Figure 2. Geographic distribution of survey respondents.*

Survey responses revealed significant trends in the following areas, each of which we will explore in this paper:

- The role of fundamental research and emerging S&T in accelerating vaccine development
- New collaborative and data-sharing efforts
- Funding and investment in vaccine R&D
- Product-focused vaccine research with end-to-end support spanning research, discovery, development, manufacturing and distribution
- Streamlined regulatory pathways
- New production methods and distributed manufacturing to increase speed and equity of vaccine distribution

## Emerging S&T Builds on a Strong Foundation of Fundamental Research

The rapid research response to COVID-19 mounted by the vaccine R&D ecosystem drew on decades of robust fundamental research in immunology, rapid genetic sequencing capabilities to quickly establish etiology and unravel pathogenesis, and on the biology of coronaviruses, particularly SARS-CoV and MERS-CoV. This all-hands-on-deck effort also made strategic use of emerging S&T: for example, nucleic acid- and viral vector-based platforms never before used in a vaccine brought to market.

Before COVID-19 struck, such platforms were being explored for use in other vaccines, including next-generation influenza vaccines (39) [see *Science, not cynicism, rules the day* ]. Together, they are employed in about 40 percent of vaccine candidates currently in clinical trials, as shown in **Figure 3**, and in 6 of 10 leading COVID-19 vaccine candidates, as shown in **Table 1** (40). These include mRNA vaccines from Moderna and Pfizer, whose recent announcements of better-than-expected preliminary Phase III results made headlines. If such ground-breaking vaccines prove safe and effective against SARS-CoV-2, knowledge and momentum gained in their development could propel progress toward a UIV.

### Science, not cynicism, rules the day

No less remarkable—but far less appreciated—than the swift development of several promising COVID-19 vaccines is the wealth of emerging science and technologies that made this phenomenon possible. Developed over years of painstaking research and refined through application to multiple vaccine targets, nucleic acid- and viral vector-based platforms had been groomed for “plug and play” creation of vaccines against emerging pathogens.

Among these is a platform recognized as a promising basis for UIV development (75). The non-replicating chimpanzee adenoviral vector vaccine (ChAdOx1) developed by Sarah Gilbert and colleagues at Oxford University, upon which they quickly built the COVID-19 vaccine produced by AstraZeneca, was previously used to create a vaccine against two conserved influenza proteins that produced long-lasting cellular immunity in a Phase 1 trial (76,77). ChAdOx1 is also the basis for a tuberculosis vaccine recently demonstrated to be safe and immunogenic in a Phase 1 trial (78).

Even closer, Gilbert and her team had developed a robust vaccine against another coronavirus, MERS (79,80). Springing into action with the SARS-CoV-2 sequence, they swiftly engineered a vaccine candidate for COVID-19; it advanced to clinical trials in April 2020, supported initially by a $2.7 million grant from the UK government, and eventually in partnership with AstraZeneca (81). Interim results of Phase II/III trials, announced in late November 2020—though complicated by methodological issues related to the conduct of those trials—confirm the vaccine’s efficacy (80,82). Ongoing Phase III trials conducted in several countries are anticipated to enroll up to 60,000 volunteers.

The power of fundamental research and discovery to solve the world’s complex challenges is no better demonstrated than in the laudable work of the many researchers seeking to counter the assault from COVID-19. Their inspiring achievements provide a roadmap for avoiding such calamity in the future—and our first destination should be universal influenza vaccines available *before* the next pandemic strikes.

**Table 1. Leading COVID-19 Vaccine Candidates**(40)

| Leading Candidates | Vaccine Categories | Clinical Phase |
|---|---|---|
| BioNTech/Fosun/Pfizer | RNA | Regulatory Review |
| Moderna | RNA | Regulatory Review |
| University of Oxford/AstraZeneca | Non-Replicating Viral Vector | III |
| Sinovac/Instituto Butantan | Inactivated Virus | |
| Wuhan Institute/Sinopharm | Inactivated Virus | III |
| Beijing Institute/Sinopharm | Inactivated Virus | III |
| Gamaleya Research Institute | Non-Replicating Viral Vector | III |
| CanSino Biologics | Non-Replicating Viral Vector | III |
| Janssen Pharma | Non-Replicating Viral Vector | III |
| Novavax | Protein Subunit | III |

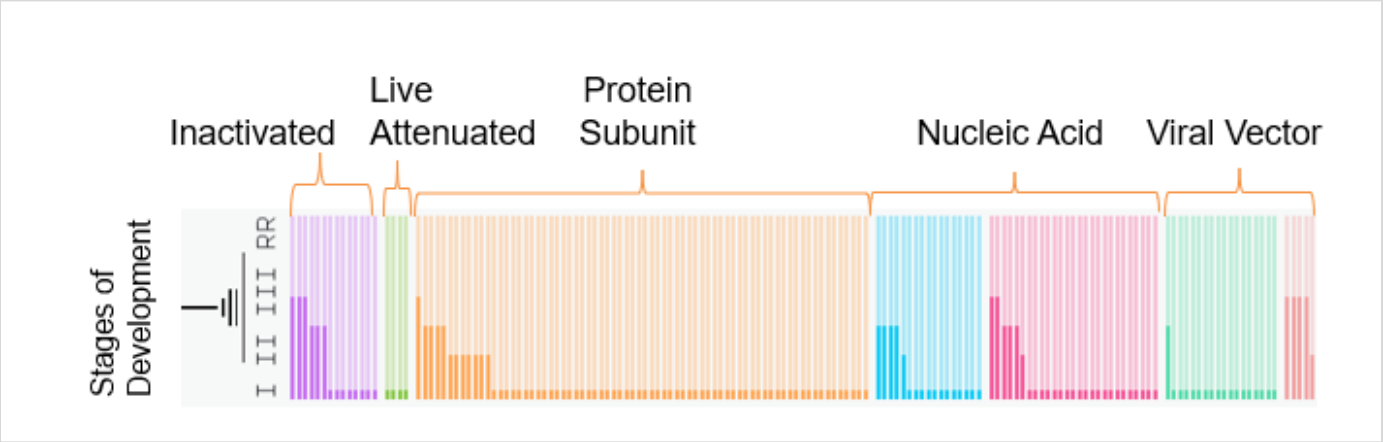



*Figure 3. The regulatory status of 237 COVID-19 vaccines, organized by technology platform, as of December 2, 2020. Two COVID-19 vaccines are in regulatory review and seven have entered phase III trials. Data from the Milken Institute* (40).

## Collaboration and Information Sharing

The title of a New York Times story from April 2020 heralds a remarkable cultural shift that may outlast the pandemic: *Covid-19 Changed How the World Does Science, Together* (24). Six months later, respondents to our survey ranked collaborative work and information-sharing as top accelerating factors in COVID-19 development that should be carried forward in order to advance other pandemic vaccines (see **Figure 4**).

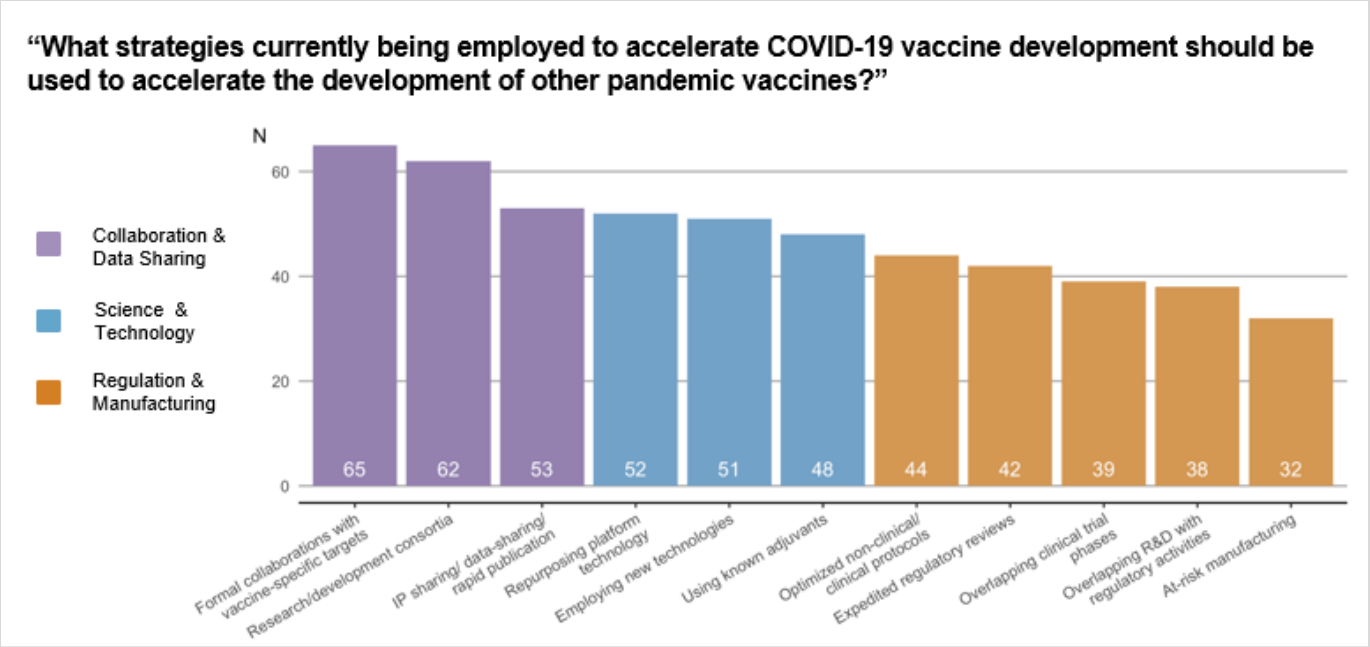



*Figure 4. Survey responses to the question, "Which elements currently being employed to accelerate COVID-19 vaccine development should carry forward to accelerate development of other pandemic vaccines?" The top three responses related to collaborative engagement: formal collaborations; consortia for research and development; and IP- and data-sharing and rapid publication.*

Interestingly, when asked a similar question specific to future UIV development, respondents ranked factors related to scientific discovery and knowledge above those related to collaboration, reflecting significant research challenges yet to be overcome to create a UIV (see **Figure 5**).

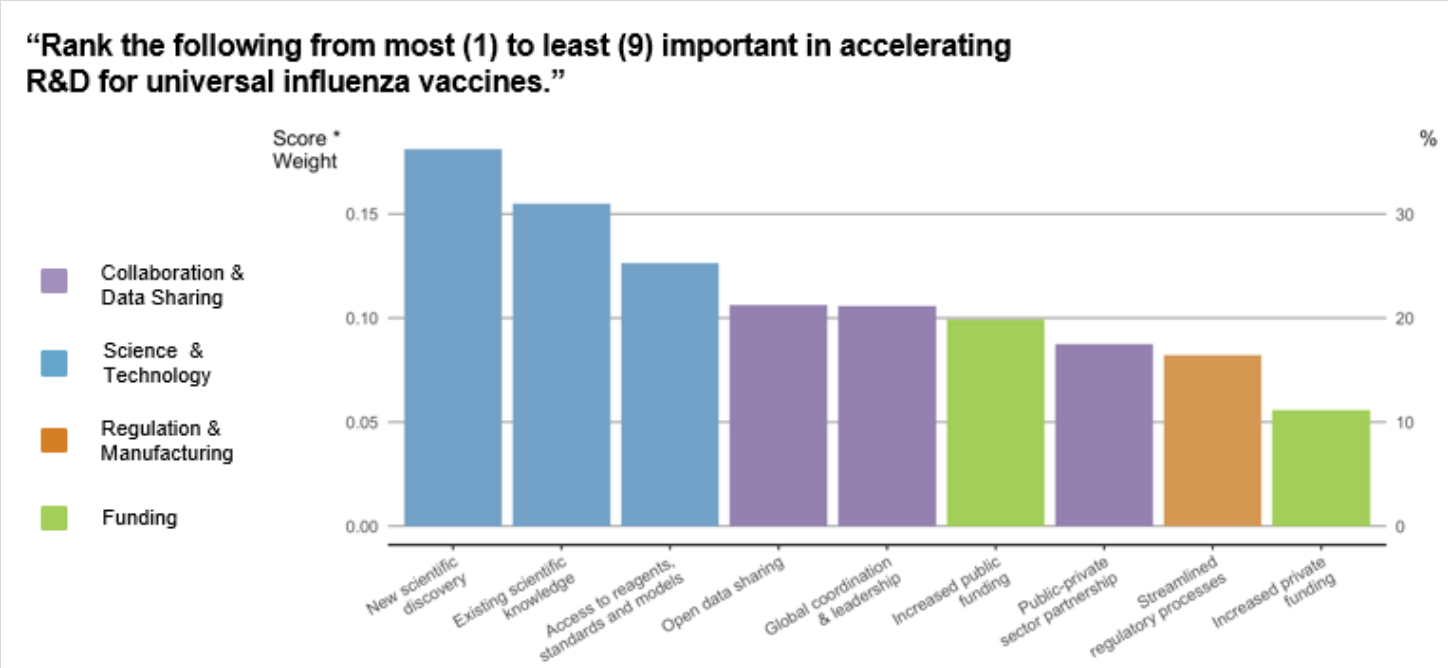



*Figure 5. Survey responses to the question shown above, among choices shown on the horizontal axis. Here, top responses reflect the primacy of gaining and applying scientific knowledge in pursuit of a UIV.*

As one survey respondent noted, "new partnership between academic institutions, public sectors and industries, along with the sharing of basic research, freely accelerated the vaccine pace against COVID-19."

Partnerships between academia and pharma and public-private partnerships have flourished [see *Novel partnerships pick up the tab, pick up the pace*].

Researchers and experts from outside the vaccine R&D ecosystem are also lending their expertise to the COVID-19 response. Thirty-seven percent of survey respondents reported that they were collaborating with representatives of fields not traditionally associated with vaccine development, including computer science, computational biology and bioinformatics, biochemistry, and physics. Forty-nine percent of organizations funding vaccine R&D prior to COVID-19 reported supporting new grantees or partners at the time of the survey. The *Academic* and *Biotech/Pharma* sectors accounted for the most reported new partnerships as seen in Figure 6. Such collaborations, which at least temporarily abandon traditional disciplinary and sectoral siloes, could inform future efforts to develop pandemic vaccines, including a UIV.

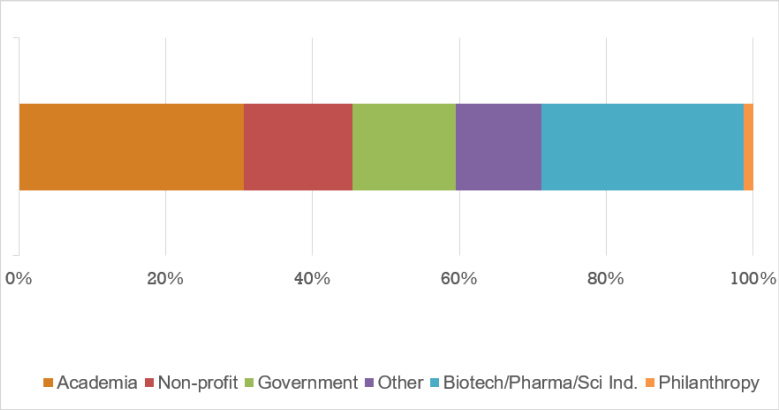



*Figure 6. Sectors reporting new partners.*

Information—grease to the wheels of collaboration—flowed with unaccustomed ease among R&D partners responding to COVID-19, and across disciplines, sectors, and borders. Because few institutions explicitly reward open and early data sharing and the tangible results it may produce, sustaining this pandemic-era cultural shift will require systemic change. For example, criteria for professional advancement in academic research, which emphasize formal publications and funding awards, tend to discourage collaborative engagement. Incentivizing data sharing for critical problem-solving, whether or not it results in publication, could enhance international and inter-sectoral scientific cooperation and, as one survey respondent wrote, move academic R&D "away from using funding to 'print scientific papers' onto encouraging finding solutions to real problems."

Seeking to identify ways to facilitate ongoing sharing of data and information, which in turn could sustain new partnership models to advance vaccine R&D, we asked survey respondents, "what professional advancement policies could institutions adopt to privilege data sharing, whether or not it results of publication?" Several responses advocated for the establishment of formal

## Novel partnerships pick up the tab, pick up the pace

Not surprisingly, the three COVID-19 vaccines farthest along the development pipeline received unprecedented levels of funding (40). However, they also benefitted from new funding structures: cross-sectoral and public-private partnerships involving academia, companies of all sizes, and direct governmental engagement.

The previously described partnership between Oxford University and AstraZeneca marked a new level of commitment on the part of industry to manufacture the vaccine, later named AZD1222, while clinical trials were still underway. A multi-partner consortium is enabling clinical development and manufacturing of the vaccine in India, as discussed below.

Collaboration between NIH researchers and Moderna,a clinical-stage biotechnology company, created the COVID-19 vaccine candidate mRNA-1273 (83); its first clinical batch was funded by CEPI. An additional partner, Lonza, will undertake larger-scale manufacturing of the vaccine, funded in part by BARDA, which also funds late-stage clinical development for this vaccine candidate.

Pharma giant Pfizer and German biotechnology company BioNTech collaborated to produce the mRNA vaccine BNT162b2, the first COVID-19 vaccine to receive an emergency use authorization (in the UK) (84). BioNTech received funding from the German government to accelerate manufacturing and development in that country (85); Pfizer funded the vaccine's global development through Phase III clinical trials, and it will deliver the approved vaccine. However, Pfizer's investment risk was significantly reduced by advance purchase commitments for the vaccine through BARDA (86).

Novel partnerships are also supporting ramped-up vaccine development aimed at providing COVID-19 vaccines for low and middle-income countries (LMICs):

- A public-private partnership between Bharat Biotech and two Indian government research institutions is developing Covaxin, currently undergoing phase III trials (87). Bharat has also licensed a novel adenovirus-based, single-dose intranasal COVID-19 vaccine from Washington University School of Medicine (St. Louis).
- The Serum Institute of India (SII) and the Indian Council of Medical Research have collaborated in the clinical development of the AstraZeneca COVID-19 vaccine candidate (known as COVISHIELD in India), and another by Novavax (88). The SII is expected to manufacture several different COVID-19 vaccines, for which they have received $150 million in support from The Bill and Melinda Gates Foundation and Gavi (89,90).

performance criteria related to collaboration and data-sharing, and one endorsed dedicated intellectual property (IP) support to facilitate the legal sharing of proprietary data.

## Funding and Investment

Multiple estimates of the economic costs of COVID-19 (16,17), calculated according to a variety of models, convey a single message: the staggering consequences of this pandemic, both acute and enduring—and far exceeding previous damage estimates for "Disease X" (41,42). Just the portion of pandemic-associated expense represented by G20 countries' spending to support their faltering economies—an estimated $10 trillion by September 2020 (43)—dwarfs the $35 billion investment required to fully fund the medical response to COVID-19, as projected by the Access to COVID-19 Tools (ACT) Accelerator, a collaborative initiative of governments, scientists, businesses, civil society, and philanthropists and global health organizations (see **Figure 7**) (32,43).

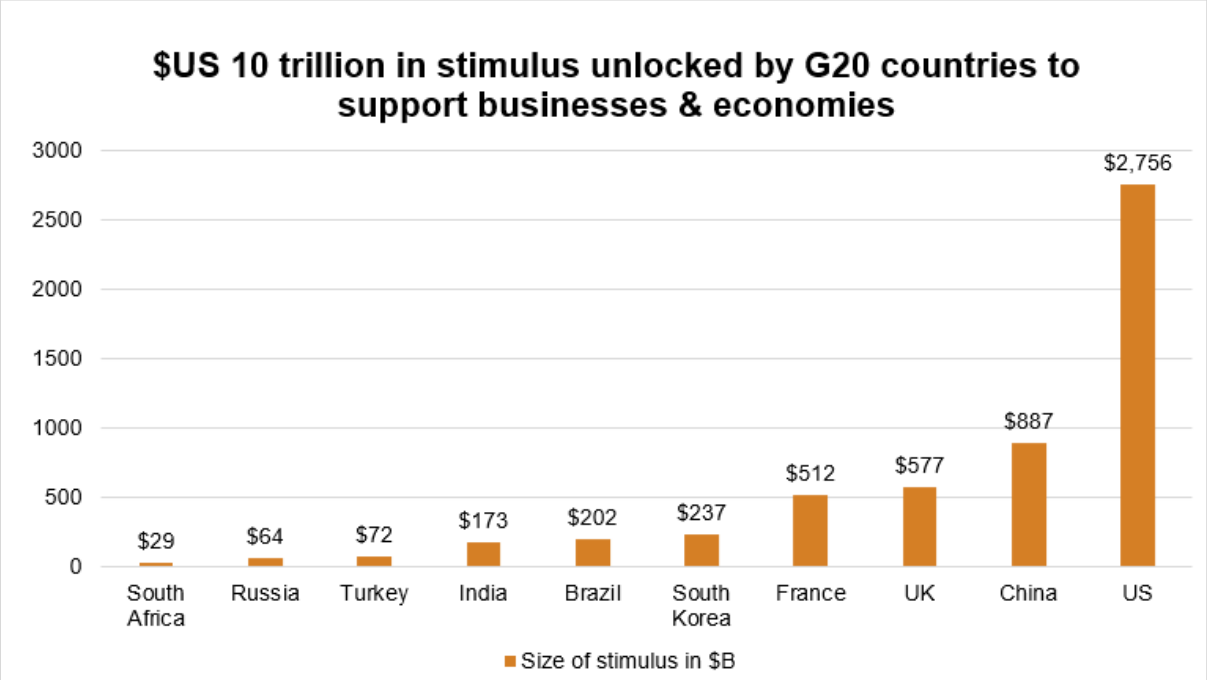



*Figure 7. Comparison of funds required for the global medical response to COVID-19 through the ACT-Accelerator with economic support unlocked by ten countries, as of September 10, 2020. Source: ACT Accelerator Investment Case & Plan* (43).

The ACT-Accelerator, which supports the development and equitable distribution of tests, treatments and vaccines for COVID-19, is one among several important public-private partnerships formed in response to the pandemic (44) (**See Figure 8).** In an effort to ensure equal access to COVID-19 vaccines, the vaccine-specific effort of the ACT-Accelerator, COVAX, created a facility that partners countries of all income levels with vaccine manufacturers (29).

A more limited initiative, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), coordinated by the Foundation for the National Institutes of Health, brings together US government agencies and departments—including the Biomedical Advanced Research and Development Authority (BARDA), CDC, U.S. Food and Drug Administration (FDA), Departments of Defense and Veterans Affairs, and the COVID-19 vaccine production and delivery effort, Operation Warp Speed (45)—with the European Medicines Agency (EMA) and representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies (46). The ACTIV vaccines working group aimed to streamline the vaccine regulatory process, including by supporting harmonized trials (47). Having completed its official charge in July 2020, the group continues to meet on an ad-hoc basis. In the future, one survey respondent noted, public-private partnerships like ACTIV could accelerate vaccine development by promoting "clinical trials with common endpoints, allowing comparisons across platforms and manufacturing at risk."

Return on investment in public-private vaccine development partnerships, relative to their potential to prevent catastrophic economic losses, is clearly vast—but could be even greater if directed toward pandemic prevention, rather than response. Thus, in addition to investigating how these partnerships have accelerated vaccine R&D, we want to learn how this momentum could be sustained to support the development of a UIV and other pandemic-preventive vaccines.

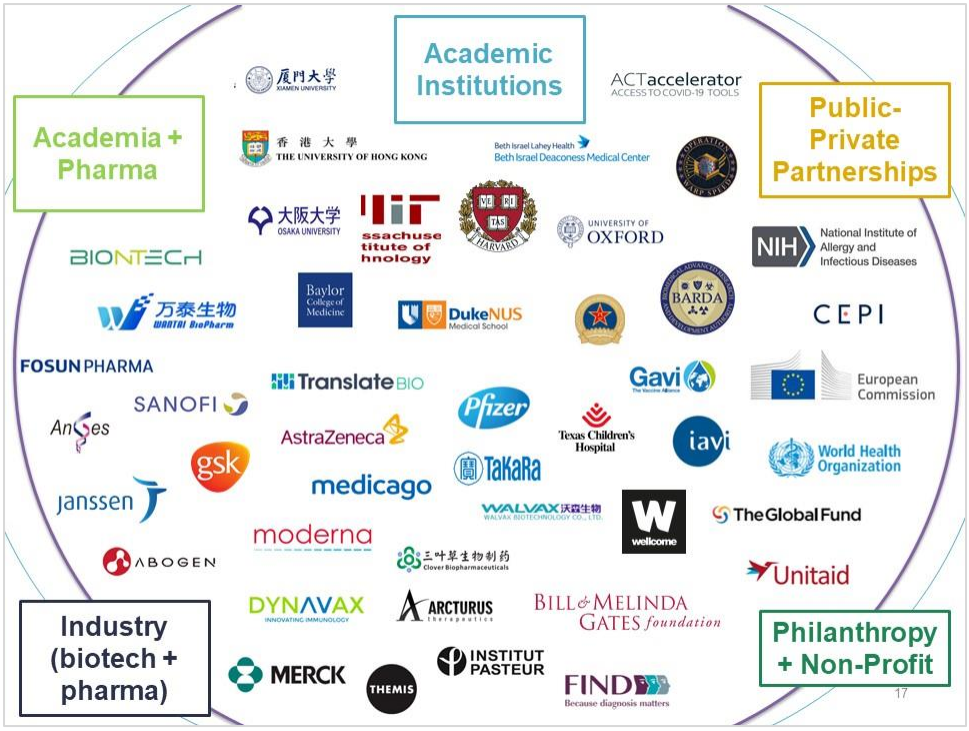



*Figure 8. Examples of partnerships formed to develop COVID-19 vaccines.*

Historically, the process of research and development for vaccines has been lengthy, expensive, and publicly funded (48,49). Only after a vaccine has proven safe, effective, and potentially profitable has a pharmaceutical company assumed the relatively low risk inherent in its manufacturing and distribution. The rapid development of vaccines against SARS-CoV-2 necessitated overriding these precedents, a transformation underwritten by governments (e.g. through programs such as Operation Warp Speed) (50), industry, non-governmental organizations including the Coalition for Epidemic Preparedness (CEPI) (51) and Gavi, the Vaccine Alliance (Gavi) (52), and philanthropy.

Our survey results suggest that the COVID-19 crisis introduced new funding entities to the vaccine R&D ecosystem. As shown in **Figure 9**, the numbers of new funding sources representing international consortia, philanthropy, private investment, and venture capital topped previous totals in each of these categories. These trends suggest that among respondents, private sector supporters of catalytic, high-risk/high-reward ventures recognize investment potential in pandemic vaccines.

This is an encouraging development, as it has long been recognized that new models are needed for financing pandemic vaccines (53). The previously described ACT-Accelerator aims to fill that and other critical needs through a purchasing collective—an approach that appeals to investors (e.g., governments, multilaterals, civil society, businesses, foundations) who expect to pay less to support a comprehensive response to COVID-19 than they would to endure an uncontrolled pandemic. It takes little imagination to extend that tradeoff to pandemic prevention, which in theory could result in far greater savings.

As an alternative to these models, Lo and coauthors (2012) designed a financing strategy aimed at reducing the risk of investing in innovative research (53–55). They propose the creation of diversified portfolios of biomedical projects at all stages of development, valued at $5 to $30 billion. Financed by a combination of equity and securitized debt, these “megafunds” could provide much-needed investment capital for vaccine research and development. “With enough programs in a portfolio,” the authors argue, “the potential revenues become more certain, more easily valued by potential investors, and more attractive from a risk-reward perspective.” This framework was recently expanded specifically to address vaccines for emerging infectious diseases (EIDs), and in recognition of the high economic value of pandemic prevention in general, as compared with the financial returns available to commercial developers of individual vaccine assets. It features a capitated vaccine “subscription” model (similar to that pioneered by CEPI), supported by public and

philanthropic funding, to compensate industry partners focused on EID vaccines, as well as megafund-like large portfolios combining multiple EID vaccines (55). This dual strategy seeks to normalize investment risk while advancing efforts to ensure global and economic health security.

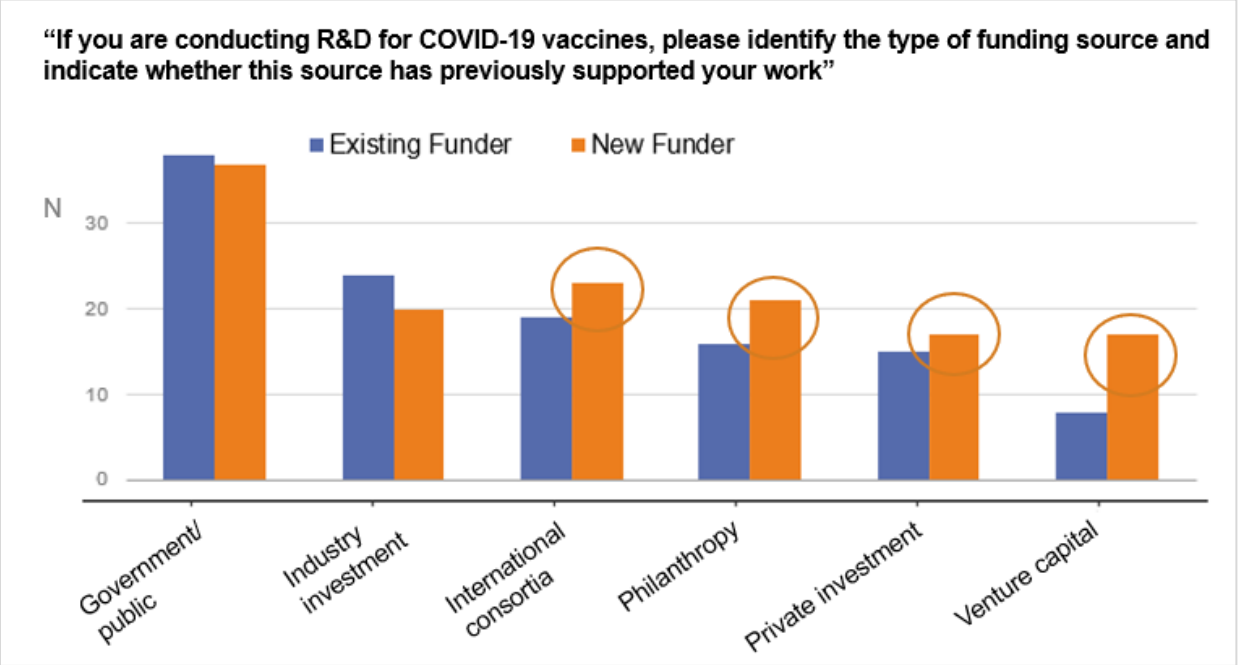



*Figure 9. Funding sources reported by survey respondents conducting COVID-19 vaccine R&D.*

## Product-focused, End-to-end Development

Scientific creativity, knowledge, and dedication were primary drivers of the COVID-19 vaccine development juggernaut that produced hundreds of diverse candidates. Responding to urgent need, coordinating efficiently, collaborating as never before, researchers and their partners across disciplines, sectors, and borders focused single-mindedly on finding the only viable exit from the pandemic: a safe, effective vaccine accessible to the entire world.

> "Investigator initiated inquiries could prove more fruitful if complemented by a structured research agenda framework designed to move research along toward a prioritized product-specific goal"

Survey respondents acknowledged this demonstration of the power of product-focused research, overwhelmingly agreeing that the same strategy could drive future pandemic vaccine R&D built, like COVID-19 vaccine candidates, on discoveries from investigator-initiated inquiry. As one respondent wrote, "Investigator initiated inquiries could prove more fruitful if complemented by a structured research agenda framework designed to move research along toward a prioritized product-specific goal." Similarly, in explaining the Wellcome Trust's recent extension of support to goal-oriented as well as basic research, director Jeremy Farrar observed that "there are certain challenges, where you can't just leave it to the idiosyncrasies of discovery…You have to have a greater sense of mission of where you're trying to get to (56)."

The record-setting pace of COVID-19 vaccine development also entails at-risk manufacturing of promising candidate vaccines, made possible by unprecedented funding strategies that have deployed resources commensurate with a global health and economic crisis. Rather than proceed through the typical linear development process, COVID-19 vaccine development is accelerated through the parallel execution of several key stages [see *Multi-tasking vaccine development*].

The so-called end-to-end funding that ensured the swift passage of COVID-19 vaccines from discovery through distribution offers a promising framework for underwriting pandemic preparedness. In their August 2020 report (57) to the Global Preparedness Monitoring Board, Keusch and Lurie advocate the creation of "a global financing system that addresses the situation of the entire world having needs for diagnostics, therapeutics, vaccines and PPE….[by assuming] the financial risks for scale up, manufacturing at risk, purchasing commitments in support of a globally fair allocation system."

Responding to the COVID-19 crisis, the vaccine R&D ecosystem has demonstrated the immense power and efficiency afforded by product-focused research, supported end-to-end—from vaccine discovery through distribution—by a cross-sectoral partner network. Notably, these proven mechanisms could be even more effective if applied to pandemic prevention; for example, by accelerating UIV development.

## Streamlining Regulatory Pathways

Many national regulatory authorities have streamlined approval processes to expedite development of COVID-19 vaccines, while international efforts to harmonize clinical trial protocols have gained momentum and are expected to further accelerate vaccine development (66,67). Typical regulatory adaptations have included:

- Relaxation of pre-trial risk assessment requirements
- Adapted trial protocols
- Enabling conduct of some trial functions by sub-investigators at local sites
- Use of electronic documentation methods
- More flexible trial oversight, including remote monitoring
- More flexible conduct of ethical reviews not involving patient safety (68)

Additional changes in regulatory and review procedures aimed at accelerating COVID-19 vaccine development have included greater collaboration between researchers and regulators; the use of risk-benefit calculations to support regulatory decision making (69); the streamlining of Good Manufacturing Practices (GMP); the acceptance of Phase IV data collection and surrogate markers toward regulatory approval; and, the application of the FDA's animal efficacy rule (in lieu of challenge trials, given the lack of therapeutics for COVID-19). Responding to concerns that the expedited regulatory pathway for COVID-19 vaccines could compromise their safety, NIH director Francis Collins sought to reassure the public. "While administrative steps are being streamlined to speed the process, safety and effectiveness measures are just as rigorous than ever," he insisted (70).

The pharmaceutical industry, stimulated by new levels of regulatory flexibility, is pressing for this to continue beyond the pandemic (71). Two-thirds of survey respondents apparently expect that to happen, agreeing that that "rapid and significant changes in vaccine R&D occurring in response to COVID-19 have the potential to permanently shift pandemic vaccine R&D." In particular, as shown in **Figure 10**, they emphasized three features of the regulatory review and approval process associated with international harmonization and collaboration as having the potential to accelerate R&D for pandemic vaccines beyond COVID-19.

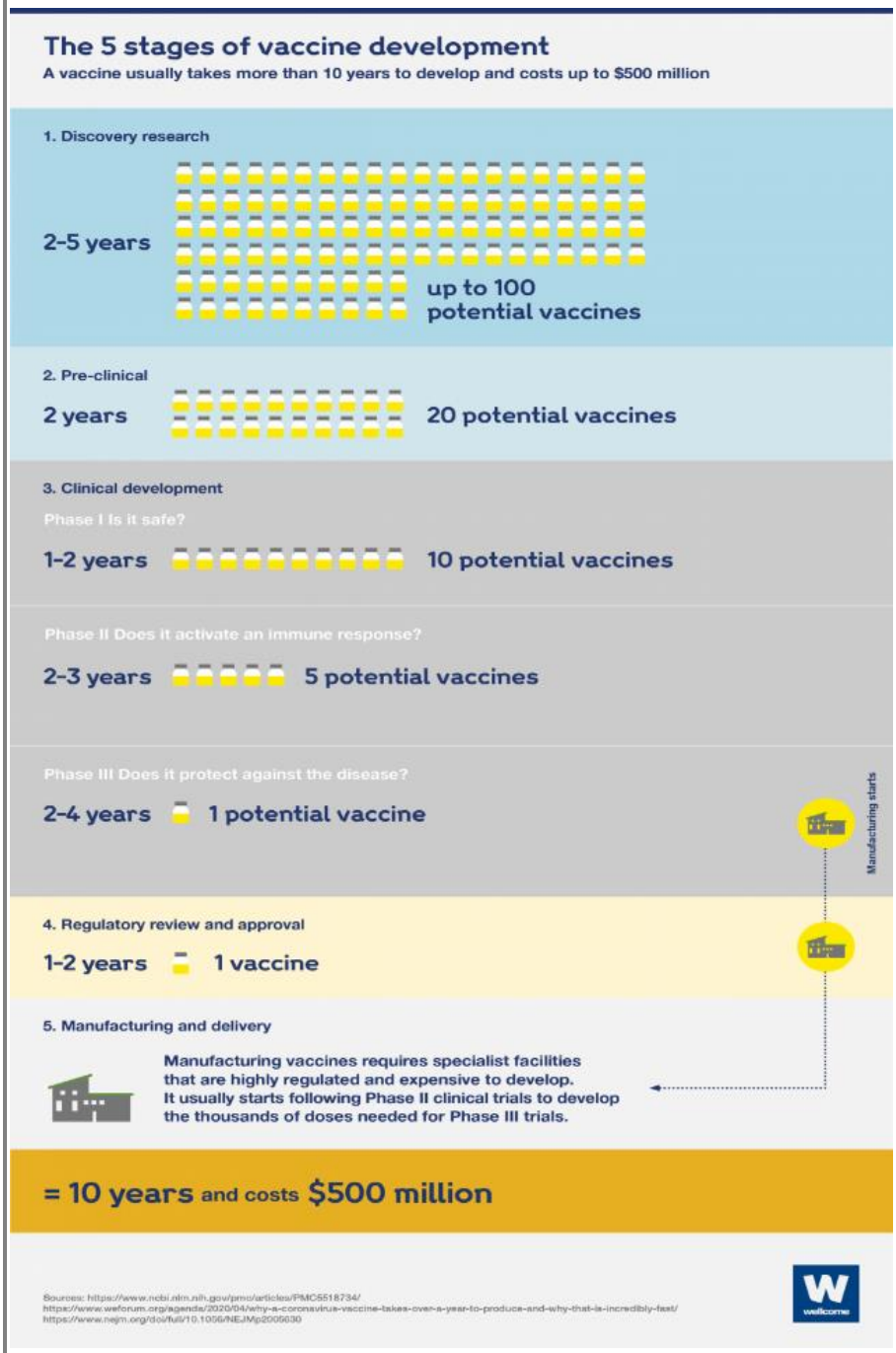
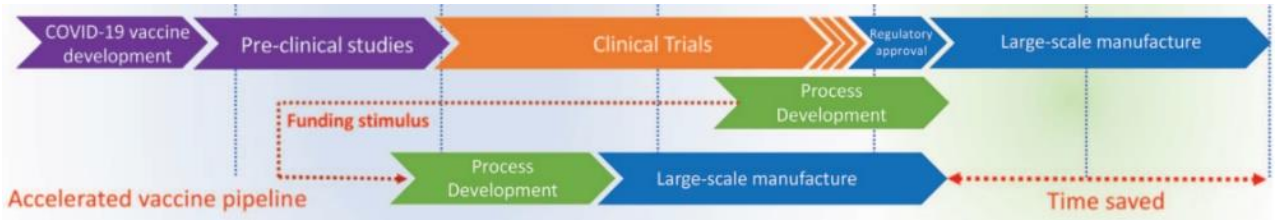



*Figure: Wellcome Trust* (58); *Data from Plotkin et al. 2017 (59), Prichep, E. World Economic Forum (2020) (60), Lurie et al. 2020 (61)*

## Multi-tasking Vaccine Development: from serial to parallel processing

The vaccine development cycle proceeds through a series of well-established stages. Moving through these stages typically occurs serially, and—for the tiny fraction of candidates that complete the process—often takes a decade or more, in large part because different stages involve different sectors (62). Academic researchers do most of the basic science and early development, usually with government support; industry (and sometimes government and/or academia) performs further applied research and clinical testing; government conducts regulatory review and approval; industry produces the vaccine and distributes it (sometimes with government assistance). Ongoing (Phase IV) studies of vaccines are generally conducted by the government, sometimes with assistance from academia or industry. The complexity, expense, and length of this process hinders innovation in vaccine R&D in general, and, in the specific case of vaccine candidates developed against SARS- and MERS-CoV, halted their development at the pre-clinical stage (63,64).

By contrast, COVID-19 vaccine development proceeded seamlessly, as intersectoral collaboration minimized delays associated with handoffs. Collaboration—as well as at-risk funding for manufacturing—also enabled key development steps to occur in parallel, hastening the availability of successful vaccines.




*Young, PR. Disease X ver1.0: COVID-19. Microbiol Aust. 2020 Jun 1; 41(2):109–12 (65)*

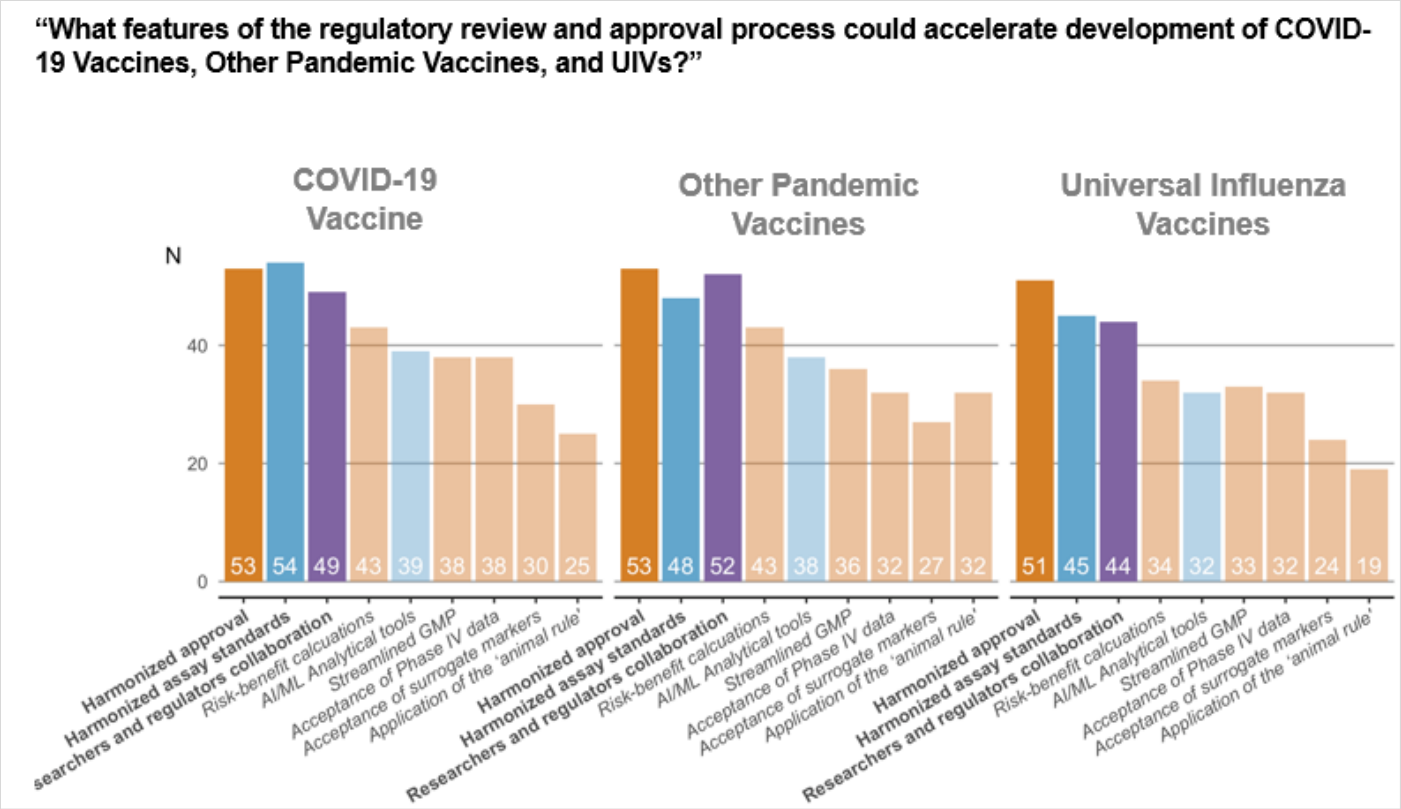



*Figure 10. Survey responses to each version of the question shown favored three features: internationally harmonized approval processes for pandemic vaccines; harmonization and standardization of assay data with biological standards and the vaccine efficacy animal study; and, greater collaboration between researchers (academic and/or industry) and regulators on pre-clinical evaluation of novel technologies or discoveries.*

"Regulatory approval of the novel technologies for COVID vaccines…will have provided additional scientific and technical experience and data that can be utilized for accelerated development of universal influenza vaccines that also utilize these technologies," wrote one survey respondent. "Thus, the regulatory pathway for approval of influenza vaccines using these approaches should be clearer to industry and to investigators using these approaches."

## Ensuring Global Access

Thanks to COVID-19, these epidemiological adages are familiar to many:

> "No one is safe until everyone is safe."

> "Vaccines don't stop disease; vaccination does."

Acting on these truths, however, remains an aspiration—even in the midst of a pandemic (72). Public health advocates have long characterized vaccines as global public goods, to which fair and equitable access must be guaranteed. The previously described establishment of the COVAX facility represents a major step toward realizing this ideal; however, at the time of this writing, it remains underfunded (73).

Moreover, as Keusch and Lurie (2020) observe, "realizing the goal that pandemic products are global public goods will likely require distributed manufacturing in multiple countries, so that no single country can seize

products made within its borders for itself (57)." To improve global access to vaccines and other pandemic products, they recommend siting manufacturing capacity in multiple low- and middle-income countries. Such facilities, they note, should be aligned with the most promising platforms available, such as nucleic acid-based vaccines, requiring supporting investments in advanced manufacturing technology and the development of robust supply chains.

Innovative, efficient vaccine production methods and technologies, employed in distributed manufacturing facilities, may increase access to pandemic vaccines, beginning with COVID-19. Novel partnerships—which could even involve bilateral agreements between competing companies—can ensure flexible, fungible vaccine manufacturing arrangements (74). Building on this foundation will significantly increase the impact of future pandemic vaccines, and the potential of a UIV to extinguish the imminent threat of pandemic influenza.

## SUMMARY AND CONCLUSION

COVID-19 offers both cautionary and encouraging lessons for the vaccine R&D ecosystem. The Influenzer Initiative recognizes that UIVs—vaccines providing protection from all influenza strains, including those with pandemic potential—offer more than pandemic *preparedness*: UIVs provide pandemic *prevention*. Our ongoing investigation of COVID-19 vaccine development aims to discover how the extraordinary momentum of pandemic response can be sustained and harnessed in pursuit of UIVs. The following findings, derived primarily from our October 2020 survey of key experts, summarize lessons learned to date:

- The advance of novel vaccine development platforms and technologies to produce safe and effective COVID-19 vaccines provides a glide path to accelerate next-generation influenza vaccine development.
- Collaboration and open data sharing have encouraged innovation and progress toward a pandemic-ending vaccine, but explicit incentives will be required to sustain current levels of collaboration, beyond the pandemic response.
- Pandemic vaccines are enormously cost-effective; a UIV capable of averting an inevitable pandemic disease would be an even greater bargain. Creative financing mechanisms can decrease investment risk necessary to promote innovation.
- Product-focused R&D, backed by a network of partners providing end-to-end support, is immensely efficient in accelerating the development of innovative vaccines.
- Regulatory pathways can be demonstrably streamlined through multiple mechanisms without compromising safety.
- Improved manufacturing methods and technologies and distributed manufacturing strategies enable equitable access to vaccines and other global public health goods.

COVID-19 has shown us how devastating a pandemic can be, and also how rapidly the vaccine R&D ecosystem can respond to such a threat. These insights must inspire action now to protect the world from the influenza pandemic we know is coming.

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## ABOUT SABIN

The Sabin Vaccine Institute is a leading advocate for expanding vaccine access and uptake globally, advancing vaccine research and development, and amplifying vaccine knowledge and innovation. Unlocking the potential of vaccines through partnership, Sabin has built a robust ecosystem of funders, innovators, implementers, practitioners, policy makers and public stakeholders to advance its vision of a future free from preventable diseases. As a non-profit with more than two decades of experience, Sabin is committed to finding solutions that last and extending the full benefits of vaccines to all people, regardless of who they are or where they live. At Sabin, we believe in the power of vaccines to change the world. For more information, visit sabin.org & influenzer.org and follow us on Twitter, @SabinVaccine & @TheInfluenzers.


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