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COVID-19 VACCINE DEVELOPMENT: BUILDING ON A LEGACY OF INNOVATION

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The SARS-CoV-2 virus at the center of the COVID-19 pandemic may be novel, but the coordinated research and development efforts to create a vaccine for it are not entirely so. They borrow from experiences derived from more than 50 years of successful vaccine development programs. At the same time, they are incorporating advances that were not available to earlier innovators – advances in science, technology, and the R&D process itself. While vaccine development for clinical indications during the mid-20th century primarily took place in public health departments and research institutions, these efforts gave way to the more modern (and largely private) efforts of pharmaceutical companies over time. Today, though, the global demands of the COVID-19 pandemic are bringing public and private forces together again.[1] The efforts to identify, manufacture, and distribute a safe and effective vaccine – in terms of research, inter-enterprise collaboration, and public funding – harken back to the early days of polio vaccine development, but when confronting a novel virus, this precedent appears to light the path that will lead most rapidly to success.[2]

FIRST PRINCIPLES

How are today's efforts to develop a COVID-19 vaccine similar to or different from efforts to develop other vaccines over the last 50 years? In terms of similarities, each effort starts with a premise that the immune system will respond to a prototypical vaccine in a largely predictable manner. In response to the presence of an antigen – historically based on a weakened version of the target virus injected into the patient – the immune system should respond with appropriately specific antibodies. Optimally, immunological memory will ensure that future exposure to the antigen stimulates the same response and continues to mitigate the replication of the virus.[3]

As in other infectious disease programs, though, developers of a COVID-19 vaccine must consider the possibility that vaccination may not convey long-term immunity. It remains unknown whether infection by SARS-CoV-2 confers lasting immunity and protects an individual against a later reinfection that would result in the development of COVID-19. In other coronavirus infection situations, reinfection remains a possibility. Exposure to seasonal coronaviruses routinely recurs every 12 months, and illness may remain a possibility even after earlier exposure.[4] For these reasons, prospective vaccine candidates will be subject to rigorous testing in animal trials before extensive human trials and safety monitoring.[5]

Yet, there is significant reason to be optimistic. Live-attenuated coronaviruses, killed coronaviruses, viral-vector vaccines, and DNA-based vaccines have all been used successfully to vaccinate against animal coronaviruses.[6] Additionally, there are specific similarities between efforts to combat the coronavirus responsible for COVID-19 and the coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS),[7] the only coronaviruses currently known to be capable of producing severe respiratory disease in humans. Each of these coronaviruses is composed of a single-stranded positive-sense RNA genome, approximately 30kb in size, that is encased by a helical nucleocapsid and an outer envelope comprised of matrix (M), envelope (E), and spike (S) proteins.[8] In the coronavirus associated with SARS (SARS-CoV), the S protein was found to elicit neutralizing antibodies and became a major target antigen for vaccine development.[9]

Given an incomplete but evolving understanding of SARS-CoV-2 biology, several vaccine candidates are being developed using additional development and testing techniques, even though some of these approaches could extend the development timeline or result in the need to use repetitive doses.[5] For

example, some developers are focusing on the spike protein and its fragments, such as the receptor-binding domain. This protein became a prime target for subunit vaccines aimed at SARS-CoV and MERS-CoV, and researchers are evaluating analogous components of SARS-CoV-2 to determine whether they can be used as vaccine targets. Other regions of the SARS-CoV-2, including S1 and S2 subunits of the spike protein and nucleocapsid proteins, may also be viable targets for vaccine development, just as they were for the SARS and MERS vaccine efforts.[7]

THERAPEUTIC APPROACHES

Historically, vaccine development has involved four platforms, reflecting different hypotheses regarding development of immunity: cross-protection, toxoid, inactivated virus, or live attenuated virus forms. Albert Sabin's oral polio vaccine, developed during the 1950s and distributed (in the U.S.) in the 1960s, relied on live attenuated strains of the polio virus, while the Salk vaccine, which was contemporaneously developed and distributed in the U.S. in 1954, relied on inactivated virus. These platforms can work well but pose challenges that are particularly accentuated when rapid vaccine development is mandated by a virus as ubiquitous and as potentially deadly as SARS-CoV-2. Specifically, vaccines built on these traditional platforms can be difficult to manufacture at scale, and to combat COVID-19, they would need to be deployed to more than 7 billion people as quickly as possible. In addition, they carry with them the risk that the virus could revert to a virulent form, which is especially problematic for highly pathogenic and incompletely characterized pathogens. This latter challenge poses both short- and long-term complications, some of which could be fatal.[10, 11]

For these reasons, several novel vaccine platforms are being explored for COVID-19, including:

- Subunit vaccines
- Nanoparticle vaccines
- Viral vector vaccines
- Nucleic acid vaccines

Subunit vaccines use recombinant viral proteins as antigens, while nanoparticle vaccines use synthetic virus-like particles as recombinant antigens. Viral vector vaccines use recombinant pseudotyped viruses to express antigen, while nucleic acid vaccines use an engineered plasmid to directly deliver nucleic acid (DNA or mRNA) encoding the antigen.[10]

Several recent vaccines have been based on these novel development approaches, thus providing a model platform for R&D efforts. Vaccines for HIV, Ebola, Zika, and Chikungunya, for example, have been (or are currently being) developed using viral vectors such as adenovirus (Ad), measles virus (MV), vesicular stomatitis virus (VSV), alphaviruses, poxviruses, and herpesviruses.[11, 12] One viral vector vaccine that has been licensed and is available for human use is a recombinant vesicular stomatitis virus for Zaire Ebola virus (rVSV-ZEBOV). Currently, no nucleic acid vaccine is licensed for human use, but several DNA-based vaccines have been approved by the FDA and USDA and are licensed for veterinary use, including an equine vaccine against West Nile virus and a canine vaccine against melanoma.[13, 14] Nucleic acid vaccines are currently under investigation targeting Ebola, influenza, and Zika virus in humans.[11, 12] Research continues into the applicability of mRNA vaccines in both personalized and generalized oncology scenarios,[15] although these vaccines typically target tumor-associated antigens that are preferentially expressed in cancerous cells, thus they are therapeutic rather than preventative vaccines.

Compared to traditional vaccine platforms, nucleic acid vaccines are seen as offering distinct advantages, and this platform has garnered the greatest attention from SARS-CoV-2 vaccine researchers.[10] DNA- and RNA-based vaccines can be manufactured quickly and at greater scale than conventional vaccines, reflecting the synthetic processes that are involved.[11] Moreover, experience with these platforms from prior and ongoing oncology vaccine therapeutics as well as early phase clinical programs in infectious diseases like influenza, Zika, rabies, and cytomegalovirus (CMV) have provided a framework that enables developers and regulators to scale up the clinical development of the mRNA vaccine development quickly and safely for COVID-19. Further, the prior nucleic acid vaccine studies inform researchers about potential attributes and liabilities belonging to this class of vaccines, which inform subsequent R&D efforts, since many of the experiences are transferable across therapeutic areas. Again, while no RNA vaccine has yet been approved by regulators, RNA vaccines have repeatedly entered clinical trials and regulators have been examining these studies for more than 20 years. This history provides a pathway forward.[5, 16]

EXTERNAL PRESSURES REMAIN CONSTANT

The challenges associated with the biology of the SARS-CoV-2 virus and of operationalizing a mechanism to protect humans from developing COVID-19 are not the only challenges developers face. The external pressures to bring a safe and effective vaccine to the world remain both significant and constant.

Revisiting and accelerating the R&D process

The SARS-CoV-2 virus belongs to a unique RNA class of viruses for which vaccine development has proven to be elusive. HIV is another such virus, and an effective preventive vaccine has eluded researchers for nearly 40 years.[1] However, the speed with which the SARS-CoV-2 virus spread across the globe has prompted developers to revisit their approaches to research and development and spurred the adoption of a variety of stratagems associated with a "fast-fail" development paradigm. The fast-fail approach may be able to reduce expected time in the pipeline, reduce development costs, increase R&D productivity, and proactively reallocate resources earlier in the development life cycle to reduce attrition rates. Fast-fail emphasizes the rapid elimination of non-viable solutions and the identification of a product warranting further investment.[17] Unlike standard clinical drug-testing trials, fast-fail development programs may use a smaller sample size to establish the promise of a target with confidence in early phase human studies of limited size.[18]

As a consequence of adopting this approach, activities that might previously have taken decades and involved the sequential execution of processes – pre-clinical testing, phased clinical trials, planned production and distribution – could be compressed into months. Where there has been experience with a platform in humans, for example, Phase 1 trials may commence in parallel while testing in animal models is still underway.[5]

And the evidence indicates that innovative R&D processes can significantly expedite programs: Both Moderna and Pfizer announced the encouraging completion of Phase 3 clinical trials for their respective COVID-19 vaccines less than one year after the first case of COVID-19 in humans was reported.[19, 20] Nor is this the only novelty about this pandemic design paradigm: With support from the Federal government's "Operation Warp Speed" initiative, multiple pharmaceutical companies, including

Moderna, Eli Lilly, AstraZeneca, and Johnson & Johnson, have begun to manufacture and mass produce their COVID-19 vaccine candidates even before definitive Phase 3 trial results have been completed and fully submitted for regulatory review.[21]

Scale of development

When it comes to scale of vaccine development and deployment, the best analog to the efforts informing the development of a COVID-19 vaccine lie in the efforts to develop the Salk polio vaccine. Clinical trials for the Salk vaccine in 1954 involved 1.8M children from the US, Canada, and Finland, the largest trial in human history. Both Salk's research and the 1954 Field Trials, as they were known, were underwritten by the National Foundation for Infantile Paralysis (NFIP), a private research organization founded by Franklin D. Roosevelt in 1938.[22] Fast forward to 2020 and the parallels with other large-scale multicenter, international studies as well as the U.S. government's Operation Warp Speed are apparent.

The international nature of these initiatives demands organizational and operational competency in multiple domains – from an understanding of differing standards of care in different nations and regions to an appreciation of regional differences in both central and local regulatory requirements for vaccine therapy studies. Data technology and a robust infrastructure designed to ensure data integrity throughout the development process are hallmarks of these initiatives. Coordinated activity across multiple vendors and many different stakeholders is emblematic of the clinical trial process.

Likewise, in a manner reminiscent of the financial support provided by the NFIP for the development of the Salk polio vaccine, Operation Warp Speed has provided billions of dollars to a small number of companies to accelerate development and reduce the financial risk that these companies otherwise would have incurred. Neither today nor during the development of the Salk polio vaccine was there any guarantee that these investments – both involving public and private funds – would result in safe and effective vaccines, yet neither effort could operate at the required scale without coordinated, national support.[2] It is worth noting that it took six years to develop, test, and bring the Salk vaccine to market, and in 1955, that was unprecedented.[22] Today, the elapsed time between the start of vaccine development and emergency approval of a candidate vaccine has been less than 12 months. How long it will take to manufacture and distribute quantities of vaccines sufficient to inoculate 7 billion people remains an open question.

Ongoing surveillance for potential long-term risk

The history of the Salk polio vaccine also carries reminders of the risks inherent in an accelerated development timeline and truncated development programs, lessons with which COVID-19 vaccine developers and FDA regulators are clearly familiar. Several batches of the Salk polio vaccine produced by Cutter Laboratories in 1955 contained polio virus that had been insufficiently deactivated. Nearly 120,000 children were inoculated with the Cutter vaccine carrying live polio virus, and some 50 subjects receiving the vaccine were paralyzed as a consequence.[22, 23] Following revision of federal vaccine manufacturing requirements, 400 million doses of the polio vaccine were safely distributed between the years of 1955–1962.[23]

There is also evidence to support that an increased incidence of Guillain-Barré syndrome (GBS) occurred as a consequence of an accelerated 1976 swine flu vaccine initiative, with an estimated attributable risk of an additional 1 case of GBS per 100,000 subjects receiving swine flu vaccinations.[24, 25] Even as recently as 2017, there is record of a Philippine dengue fever vaccine inducing hemorrhagic dengue syndrome in dengue-naive recipients who subsequently contracted a natural dengue virus.[26] This is owing

to the antibody dependent enhancement (ADE) phenomenon in which existing antibodies within the host may facilitate viral infection and enhance inflammation, making a second dengue infection markedly more severe than the first.[27] Given this, the World Health Organization now recommends that only individuals who have had previous dengue virus infection (dengue-seropositive individuals) receive the vaccination.[26]

Awareness of these potential complications has prompted regulatory agency and industry leaders to be vocal in their campaigns to assure the public that the most stringent safety standards and protocols are being observed as pharmaceutical companies pursue a COVID-19 vaccine along an accelerated timeline.[28] In June 2020, the FDA issued guidelines to industry outlining key considerations in the areas of chemistry, manufacturing, and controls; clinical trials; toxicity studies; post-licensure safety evaluations; and more.[29] The guidelines reflect a commitment to current best processes in the areas of testing, manufacturing, and distribution, and a commitment to facilitating the accelerated delivery of a vaccine that is safe and effective for all populations, specifically referencing many population groups that traditionally have been underrepresented in trials, such as racial and ethnic minorities, elderly individuals, and individuals with medical comorbidities.[29]

Likewise, the guidance recommends that sponsors consider early in their development data to support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy, as well as plans for pediatric assessment.[7] FDA leaders have also reminded pharmaceutical industry leaders of the importance of early engagement with pharmacovigilance agencies such as the FDA's Vaccine Adverse Event Reporting System and the Sentinel Initiative to ensure ongoing monitoring of the health and well-being of those given a vaccine.[28, 30, 31]

TABLE 1: COVID-19 AND PREVIOUS VACCINE DEVELOPMENT PROGRAMS

DIFFERENCES	SIMILARITIES
Unparalleled speed of research, industry collaboration, and government funding, as opposed to historical research initiatives sponsored by municipal or state health departments or research institutions	Basic principles of vaccine development hold true for COVID-19, particularly in terms of longer-term surveillance for untoward effects across larger and more diverse populations
Relatively novel vaccine platforms and methods utilized for COVID-19, as opposed to live attenuated strain or inactivated viral platforms	Possible similarities with SARS and MERS vaccine programs in vaccine design, strategy, and adverse event profile
COVID-19 belongs to an RNA class of viruses with limited precedent regarding immediate and longer-term clinical effects	Stringent, established safety and regulatory standards employed in both preclinical and clinical stages
New paradigm of fast start and fast-fail R&D executed in parallel, rather than sequentially as might be envisioned in the traditional R&D program	Similarities with previous vaccines in terms of platform (SARS-CoV, HIV, Zika, Ebola), speed of development, scale (polio), and risk mitigation (polio, swine flu, dengue fever)

JUST ON THE HORIZON

The degree to which the current coronavirus pandemic has already disrupted economies and societies, combined with the stress it has placed on the international healthcare infrastructure, interpersonal relationships, and even family dynamics, has called for some of the most accelerated vaccine development efforts ever seen. These efforts have adopted pathways both that map into historical vaccine R&D processes and that veer into the realm of novel accelerated stratagems (informed by appropriately conservative surveillance). They involve public/private partnerships and fast-tracked trials and regulatory review while simultaneously involving unprecedented efforts to ensure both near- and long-term safety with accelerated methods of distribution in as appropriately diverse populations as possible. They represent a combination of deep understanding and respect for biology, epidemiology, the R&D process itself, and the possibilities afforded by new scientific and technical breakthroughs.

Both the successes and the failures of the past stand as guideposts that continue to inform present-day development efforts, and recent promising announcements from Moderna and Pfizer, achieved in record time, bode well for large-scale population administration.[19, 20]

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