Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

The development of COVID-19 vaccines in the United States: Why and how so fast?

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"Why so fast?" "Are corners being cut?" "Is the vaccine safe?" These are the questions that we have heard almost every day since COVID-19 vaccine development began in January 2020 in response to the pandemic that has ravaged the world. For the last year, we have been living in unprecedented times, and with unprecedented disruption of our daily lives has come scientific innovation, unparalleled motivation and creativity, and a sense of duty to stop the pandemic and mitigate its negative economic impact through vaccination. This has resulted in the acceleration of all aspects of COVID-19 vaccine development, including vaccine formulation, clinical trials, manufacturing, and regulatory review. Several COVID-19 vaccines are now available and being used to vaccinate millions of persons around the world. The extraordinary speed of COVID-19 vaccine development—from identification of the virus's genetic sequence to the first doses being administered to the general public in less than 11 months—is due to several factors. This article focuses primarily on the speed of development of vaccines recently approved in the United States (US).

1. Past vaccine knowledge & new technology

A key element in the accelerated development of COVID-19 vaccines has been the ability to apply the extensive vaccine-development experience of industry and academia. Vaccine development is not new, nor is the process and pathway to licensure, both being well defined. Industry has been developing and licensing vaccines for many decades, and that expertise was quickly tapped in support of COVID-19 vaccine development.

The state of vaccinology has substantially evolved in the last 20 years, especially in the last 10 years, resulting in several new platforms/modalities that have been used in the development of the more recently licensed vaccines. Platforms used for licensed vaccines or in the development of new vaccines were rapidly revamped for COVID-19 vaccines. Viral vector-based vaccines, either replicating or nonreplicating (used most recently for dengue and Ebola vaccines), and recombinant protein-based vaccines (e.g., hepatitis B or human papillomavirus) were rapidly pursued. In addition, genetic vaccine technology, which has been in development for nearly 30 years, was used to develop several COVID-19-vaccine candidates, including mRNA and DNA-based vaccines [1]. In contrast to previously licensed vaccines, these nucleic-acid-based vaccines have the advantage of shorter lead times for manufacturing and more easily scalable production.

Although SARS-CoV-2 was a new coronavirus first identified in 2019, coronaviruses (which usually cause mild to moderate upper respiratory tract illnesses including the common cold) have been studied since the 1960s [2]. Two coronaviruses, SARS-CoV1 and MERS-CoV, both causing serious illness and death, emerged from animal reservoirs during the past two decades [3]. These viruses share many common characteristics with the SARS-CoV2 virus that causes COVID-19. SARS and MERs became the focus of extensive vaccine development, and several investigational vaccines entered clinical trials [4–5]. The research conducted on these viruses and the development of investigational MERS and SARS vaccines served as a foundation for the development of SARS-CoV2 vaccines.

2. Rapid response to outbreaks/pandemics

Rapid development of new vaccines in the face of an outbreak or pandemic is not unique to COVID-19. When the US was in the midst of a polio outbreak in the mid-1950s, multiple vaccine manufacturers quickly developed vaccines that would help protect the world [6]. When the Asian influenza pandemic of 1957 was first predicted, six US-based vaccine manufacturers were quickly engaged to develop and produce vaccine. Within short order, more than 40 million doses were distributed in the first few months of the beginning of the influenza pandemic, avoiding massive disease [6]. A similar response occurred during the 2009–2010 H1N1 pandemic when four different vaccine manufacturers rapidly developed and produced over 162 million vaccine doses [7–8]. The response has been the same for COVID-19 in 2020–2021, only the number of vaccine developers was 30–50 times greater.

3. Scientific collaboration/partnerships

The massive impact of the pandemic on human lives and the global economy has promoted the development of strong national and international scientific and technological collaborations rarely seen in the past. With the recognition that 10–11 billion doses

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would be needed worldwide (assuming a two-dose regimen, excluding booster doses) and that some vaccine candidates would likely not succeed, it was critical that multiple vaccine candidates be pursued [9,10]. The collective focus of researchers around the world resulted in more than 200 vaccine candidates being created within months after scientists in China first shared the genetic sequence of the novel coronavirus on January 12, 2020 [9,11,12]. In the pursuit of a COVID-19 vaccine (and other vaccines), several successful collaborations ensued. The first successful vaccines in the US and Europe were developed by partnerships, including academics partnering with industry (e.g., Oxford University/Astra Zeneca), industry partnering with industry (e.g., Pfizer/BioNTech), and government partnering with industry (e.g., Moderna/National Institutes of Health).

4. Funding

Funding for COVID-19-vaccine research and development has been unparalleled in history. Governments, bilateral and multilateral organizations, nongovernmental organizations (NGOs), and the private sector rapidly recognized the need for the funding of extensive vaccine research, development, manufacturing, and clinical trials to rapidly advance several vaccines to meet global demand. Funding for vaccines studied in the US was provided by several organizations/governments, including but not limited to the Coalition for Epidemic Preparedness Innovations (CEPI), the Biomedical Advanced Research and Development Authority (BARDA) of the U.S. Department of Health and Human Services, the German government, the Wellcome Trust, and the UK Department for International Development [13–17]. As part of Operation Warp Speed, six companies (AstraZeneca, Johnson & Johnson, Moderna, Novavax, Pfizer/BioNTech, and Sanofi/GSK) were funded or contracted by the US government based on their use of advanced vaccine technology and the status of their research [14]. In total, these companies received >$12 billion to support basic and clinical research and/or to manufacture vaccine at risk in exchange for delivery of millions of doses by a predetermined target date [13]. With such a large level of funding, vaccine development swiftly proceeded without unnecessary financial or bureaucratic delays.

5. Clinical trials

Numerous clinical trials to assess the safety, immunogenicity, and efficacy of the leading vaccine candidates were essential in determining which vaccines could be brought to market. For any COVID-19 vaccine to be well-accepted for mass vaccination of the general public, it was critical that no steps be skipped in evaluating the safety or the efficacy of the vaccine candidates. In order to do so, a combination of standardized procedures and innovative techniques was employed.

5.1. Standard research principles followed

First and foremost, key principles for the conduct of clinical research were enforced and not circumvented. Rigorous scientific methods were followed, both in the design and conduct of the clinical trials. As with any clinical trials in humans, study protocols and consent forms were reviewed by local Institutional Review Boards (IRBs) and the Food and Drug Administration (FDA) and other regulatory agencies before trials were initiated. Appropriate informed consent and protection of subject rights (as described in the Declaration of Helsinki) were enforced. Compliance with Good Clinical Practices, the traditional guidance for any research study involving human subjects, was required and strictly followed.

5.2. Study size

Clinical trial sizes were not reduced. The large-scale COVID-19 efficacy and safety studies involved 30,000 to 45,000 subjects (randomized either 1:1 or 2:1 vaccine to placebo) to ensure adequate power to detect statistical differences in disease in vaccine versus placebo recipients [18–20]. To put the size of these studies in perspective, safety and efficacy for other vaccines that have been licensed was demonstrated in clinical trials ranging from ~1000 subjects for varicella and hepatitis A vaccines, ~70,000 for rotavirus vaccines, ~5000 for *H. influenzae* vaccine, and ~15,000 for the more recently approved zoster vaccine [21–27].

5.3. Safety follow-up

"A high degree of safety is a primary goal for any widely used vaccine" [10]. Each subject in every COVID-19 study was followed for safety. This included daily reporting of postvaccination events for the week after vaccination, as well as longer follow-up (up to 2 years) for more serious events. An independent Data Safety Monitoring Board (DSMB) was convened; the sole responsibility of this board was to conduct multiple reviews of safety data in each trial to ensure that no harm was done to study participants and to stop any study in which the results were futile.

5.4. Parallel conduct of trials

While standard processes were followed for the design and conduct of clinical trials, innovation played an important role in expediting study conduct. One of the key elements that allowed clinical trials to be completed more rapidly than in the past was performing clinical trials in parallel rather than sequentially. This was accomplished by overlapping the timing of Phase 1, 2, and 3 studies. Agreement with regulators was critical in defining what information was necessary to proceed to the next step of development. For example, rather than waiting to complete the entire Phase 1 study before going on to Phase 2, Phase 2 was initiated once there was sufficient safety data from Phase 1 to reduce the risk of starting Phase 2. In addition, some preclinical studies in animals were performed in parallel with the Phase 1 studies.

5.5. Standardized protocols & data safety monitoring board

Another way in which time was saved in the conduct of critical safety and efficacy trials was through the use of harmonized protocols, a single IRB, and a single DSMB across trials of vaccine candidates from several different manufacturers. Rather than having each US vaccine manufacturer develop their own study protocols for efficacy (including defining criteria for COVID-19 cases, agreeing on statistical criteria to demonstrate efficacy, and engaging the FDA to obtain approval for the study design), a master study protocol was developed by a public–private partnership called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), established to develop a coordinated research strategy [28,29]. This protocol was adopted by five of the US COVID-19 vaccine manufacturers in their pivotal safety and efficacy trials. Key elements of this protocol were followed consistently across manufacturers, though some changes were made to suit individual needs. Use of a single DSMB eliminated the need for each company to spend time and resources identifying experts, contracting them, and establishing SOPs. A single DSMB assured consistency in the quality and frequency of data review, a lack of any perceived bias, and standardized measures to ensure subject safety across multiple vaccine candidates.

5.6. Site selection using CDC's COVID-19 vaccine tracker and modeling

Rapid identification of study sites with a high rate of COVID-19 infection, along with modeling where future waves of the pandemic might occur, helped expedite study completion, especially for the large-scale efficacy trials. In the US, use of the Centers for Disease Control and Prevention's (CDC) ongoing COVID-19 disease tracker, a timely tool to assess the evolving epidemiology of COVID-19, assisted in the selection of trial sites based on where the disease was highest, thus allowing an earlier identification of COVID-19 outbreaks and the cases needed to demonstrate efficacy (since most trials were case driven) [30]. Identification of multiple sites per study (more than 100 in some studies) as well as use of international study sites further expedited enrollment.

5.7. COVID-19 prevention network as a critical partner in study enrollment

In the US, the National Institute of Allergy and Infectious Disease (NIAID) of the National Institutes of Health (NIH) established the COVID-19 Prevention Network (CoVPN) to help enroll thousands of volunteers for the large-scale Phase 3 clinical trials [31]. The network includes four existing NIAID-funded clinical-trial networks (i.e., HIV Trials Network, HIV Preventions Trial Network, Infectious Diseases Clinical Research Consortium, and the AIDS Clinical Trials Group), all with significant infrastructure and expertise in the conduct of clinical trials.

Study enrollment was expedited in several ways. First, the CoVPN Volunteer Screening Registry was established whereby volunteers could sign up online to participate in a clinical trial. The COVPN's challenge was "we need thousands of volunteers ready to roll up their sleeves by the end of 2020!" [31] Standardized slide decks, recruitment tools, and even large-print materials for seniors were generated by the COVPN to assist in recruitment. Many study subjects were identified by the registry, and study sites could contact local volunteers who were a good match for a particular study. Interest in study participation was surprisingly high. Many individuals were simply motivated to volunteer to participate in clinical trials out of concern for the disease, the possibility of exposure to COVID-19 in the workplace, for the benefit of mankind or science, or a combination of these factors.

The CoVPN also established a national faith-based program, the CoVPN Faith Initiative, recognizing the important role that such groups play in nurturing hope, healing, and health within communities [31]. The purpose of this group was "to enhance trust and meaningful engagement in key communities throughout the US and provide accurate and updated information about COVID-19 and CoVPN clinical trials," and support of COVID-19 research studies. These efforts were particularly important in ensuring a diverse population of study participants. The CoVPN also established a community-engagement model to address community education, recruitment, and retention.

6. Manufacturing

Producing billions of doses of vaccine prior to licensure is a highly risky and costly venture for a manufacturer. All vaccines, including those authorized under an Emergency Use Authorization (EUA), must be manufactured in accordance with the international standards for Current Good Manufacturing Practices (cGMP) [32,33]. Manufacturing vaccines is a uniquely demanding process that requires consistency in quality control, and scaleup of the process to ensure continued manufacturing of a large number of vaccine doses can be a challenging and time consuming process. In order to expedite the availability of COVID-19 vaccines as soon as they were authorized, the US government and several other governments funded, at risk, the manufacturing of the most promising vaccine candidates. Once early clinical results were available, billions of government dollars were invested to allow manufacturers to enhance their biomanufacturing infrastructure and to commence vaccine manufacturing, thereby increasing the probability of millions of vaccine doses being immediately available following regulatory authorization. Iimportant investments also were made in vial and syringe manufacturing and engagement of critical contract manufacturing facilities to increase vaccine capacity.

7. Regulatory

The US FDA, as well as other regulatory agencies (e.g., Health Canada, European Medicines Agency), played an important role in expediting the review and approval of COVID-19 vaccines while continuing to maintain unwavering standards for accurate data, product quality, and safety. Early in the pandemic, extensive guidance documents were issued by the FDA and other agencies to clarify for manufacturers the pathway to licensure [34–43]. While the regulatory pathway to licensure of a COVID-19 vaccine was differently named in various countries (e.g., EUA in the US, Interim Order in Canada, and a Conditional Marketing Authorization in the European Union), the criteria for approval were fairly similar. All of the guidance documents clearly stated that safety and efficacy would need to meet the usual high standards for any licensed vaccine. Clinical trials were required to meet the same rigorous statistical endpoints for efficacy for previously licensed vaccines and to provide sufficient safety data on all subjects. In the US, a 2-month median safety follow-up on >3000 subjects in the large-scale efficacy trials was required for EUA authorization, the time period within which most adverse events occur after any vaccination [34,35]. As stated by Peter Marks, Director of the Center for Biologics Evaluation and Research at the FDA, "the agency's guidance on COVID-19 vaccines helps the public understand our science-based decision-making process that assures vaccine quality, safety and efficacy for any vaccine that is authorized or approved" [44]. The US also continued to follow its standard process of convening an independent expert panel (The Vaccines and Related Biological Products Advisory Board) to provide advice to the Commissioner of Food and Drugs on the safety and efficacy of any vaccine before being authorized under an EUA [45].

Regulatory authorities introduced innovative and agile procedures to expedite the regulatory review process for a COVID-19 vaccine. Examples of ways in which these regulatory agencies worked with industry to help speed up vaccine development and approval of COVID-19 vaccines included fast-track designation in the US (used to expedite the review of new drugs and vaccines intended to treat serious or life-threatening conditions that can address unmet medical needs), rapid scientific advice with no fees or pre-specified submission deadlines in the EU, and shorter time intervals for regulatory review. The FDA engaged in more informal discussions with manufacturers rather than waiting for a typical formal meeting (such as a Type C meeting) that could take months to schedule. The rolling review of regulatory documents allowed agencies to continuously assess the data needed for approval rather than wait for the manufacturer to submit all data only after all of the clinical trials were completed. More staff were assigned to the review and approval of COVID-19 vaccines. Inspection of the vaccine-manufacturing facilities early in the development process allowed for earlier resolution of any potential quality issues.

8. Continued assessment of safety and efficacy after EUA

Assessment of the safety and effectiveness of COVID-19 vaccines being used in the US has not stopped now that several EUAs have been issued. As with other approved vaccines, evaluation of the safety of the currently authorized COVID-19 vaccines is being closely followed through the following mechanisms: the Vaccine Adverse Event Reporting System (VAERS), which is comanaged by the CDC and FDA; the Vaccine Safety Datalink (VSD), which is run by CDC; and a unique safety system that was established specifically for this vaccine, called vsafe, which allows all persons vaccinated under the EUA to report side effects on a mobile device [46]. Vaccine manufacturers are required to submit monthly safety-update reports to the FDA as a means to ensure that all safety data are reported and reviewed in rapid order.

The effectiveness and long-term protection afforded by the available COVID-19 vaccines will now undergo further assessment at the population level through ongoing postlicensure studies agreed upon as a condition of an EUA. These data will be extremely important to assess durability of protection and waning of immunity. This information, along with the safety data described above, will allow the FDA, the CDC, and state and local health departments to routinely assess the benefits and risks of vaccination in the context of this evolving pandemic. The data also play an important role in assuring health care providers and vaccine recipients of the safety and effectiveness of COVID-19 vaccine when used in routine practice.

9. Summary

Was the development of COVID-19 vaccines now available in the US fast? *Yes.* Were corners cut? *No.* While the development timeline for the COVID-19 vaccines currently now available in the US was clearly shorter than any other vaccine, the speed of the response to the COVID-19 outbreak was driven by the recognition of the societal magnitude of the danger posed by the SARS-CoV-2 virus, the single largest threat to the health of the globe in our lifetimes. Both existing and new vaccine technologies were leveraged to shorten lead times and increase efficiency. Studies were rapidly designed and enrolled thanks to a plethora of volunteers and investigators motivated by a determination to defeat the virus. Paradoxically, the number of cases of COVID-19 required to assess vaccine efficacy was rapidly reached given the fact that the pandemic yielded a remarkably high attack rate of disease. This allowed for clear, unassailable conclusions about the vaccine's ability to prevent disease. Vaccine safety was carefully assessed, both in terms of number of study participants and the duration and quality of follow-up. Corners were not cut; rather, advanced technology, swift study enrollment, and significant funding combined with high disease attack rates resulted in some of the fastest, high-quality vaccine research ever conducted.

According to the CDC, "widespread vaccination against COVID-19 with highly effective vaccines represents a critical tool in efforts to control the pandemic and save lives" [47]. The successful acceleration of the development of several vaccines now available for use under EUAs in the US has the potential to reduce the significant morbidity and mortality associated with the SARS-CoV2 virus and bring the pandemic under control, saving lives and removing a major threat to the global economy [48].

The research and development process for COVID-19 vaccines has been transformative and was essential in the face of the greatest public health threat the world has faced in over a century. Key to this process has been scientific focus and the funding of technology, research, and manufacturing capacity. The extraordinary improvements and achievements in vaccine development identified in the last year have been highly successful and are a reassurance that when the next pandemic occurs, we should be able to respond even faster—thanks to the lessons learned here.

10. Disclosure statement

Dr. Kuter is a consultant for Moderna.

Dr. Offit has no activities to disclose.

Dr. Poland is the chair of a Safety Evaluation Committee for novel non-COVID investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on non-COVID vaccine development to Merck & Co., Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Dynavax, Genentech, and Genevant Sciences, Inc. Dr. Poland has offered consultative advice on COVID vaccine study design and safety to Eli Lilly and Company, Janssen Global Services LLC, and AstraZeneca. Dr. Poland holds patents related to vaccinia and measles peptide vaccines. Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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