Perspective

Accelerated COVID-19 vaccine development: milestones, lessons, and prospects

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SUMMARY

The development of effective vaccines to combat infectious diseases is a complex multi-year and multi-stakeholder process. To accelerate the development of vaccines for coronavirus disease 2019 (COVID-19), a novel pathogen emerging in late 2019 and spreading globally by early 2020, the United States government (USG) mounted an operation bridging public and private sector expertise and infrastructure. The success of the endeavor can be seen in the rapid advanced development of multiple vaccine candidates, with several demonstrating efficacy and now being administered around the globe. Here, we review the milestones enabling the USG-led effort, the methods utilized, and ensuing outcomes. We discuss the current status of COVID-19 vaccine development and provide a perspective for how partnership and preparedness can be better utilized in response to future public-health pandemic emergencies.

Introduction

The first case report of novel coronavirus 2019 (2019-nCov) in the United States was published on January 31, 2020 in the *New England Journal of Medicine* (Holshue et al., 2020). In the year and a half since, over 34.4 million cases have been diagnosed with the now recognized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), and over 608,000 lives have been lost in the United States (CDC, 2021c). Around the globe, the figures are more devastating, with over 195 million cases reported and greater than 4.1 million deaths (JHU, 2021). The adverse impact of this pathogen concerns not only global public health but also the economic status of nations and individuals (Cutler and Summers, 2020). Not since 1918 has the world been so affected by the emergence, spread, and death toll resulting from a respiratory virus (Taubenberger et al., 2000; Wei et al., 2020). The exponential rate of disease spread seen in early 2020 and related case projections demanded a comprehensive response that included the public sector working in tandem with private industry to develop prevention and treatment approaches for this new disease.

Fundamental to the response was the development of vaccines capable of thwarting COVID-19 disease, hospitalizations, and associated deaths. The US government (USG), working closely with pharmaceutical, biotech, and academic collaborators, set forth a plan to capitalize on several decades of progress on new vaccine platforms, viral immunology, structural biology, and protein engineering research, along with clinical trial operations expertise to enable the rapid development, evaluation, manufacturing, and deployment of successful vaccines. Also important to note was the "Determination of Public Health Emergency" made on February 4, 2020 by the US Secretary of Health and Human Services (HHS) declaring there to be a "a public health emergency that has a significant potential to affect national security or the health and security of United States citizens

living abroad and that involves a new coronavirus (2019-nCoV)" (Health and Human Services Department, 2020). The federal notice also outlined the criteria under which emergency use authorization (EUA) could be issued. In less than 1 year from pathogen identification, multiple vaccines have received EUA from the US Food and Drug Administration (FDA), enabling widespread vaccine administration to begin during a public health emergency (Figure 1).

Nearly 6 months post authorization, as the vaccination campaign continues for the general US population, vaccine research remains ongoing to define durability and indications for boosting and to assess vaccine safety and immunogenicity in pediatric and special populations. Basic and clinical research on the epidemiology, transmissibility, pathogenicity, and antigenic and immune evasion properties of emerging SARS-CoV-2 variants is also continuing. To adequately prepare for the emergence of subsequent pathogens and to establish medical countermeasures for known and unknown viruses with pandemic potential, it will be important to further incentivize comprehensive preparedness programs, including improved global surveillance and the development of diagnostics, vaccines, and therapeutic products for the major viral families known to infect humans.

This COVID-19 vaccine development perspective will review the tools of modern vaccinology employed to combat a novel pathogen, the critical steps taken as part of the USG response (initially known as Operation Warp Speed [OWS]), and the collaborative mechanisms utilized for industry partnerships and efficient clinical trial conduct. Additionally, we discuss lessons learned and propose future approaches to improve pandemic preparedness and response.

Modern vaccinology: Structure-guided vaccine design

The advances in technology supporting modern vaccine design have been driven by the need to tackle challenging viral diseases
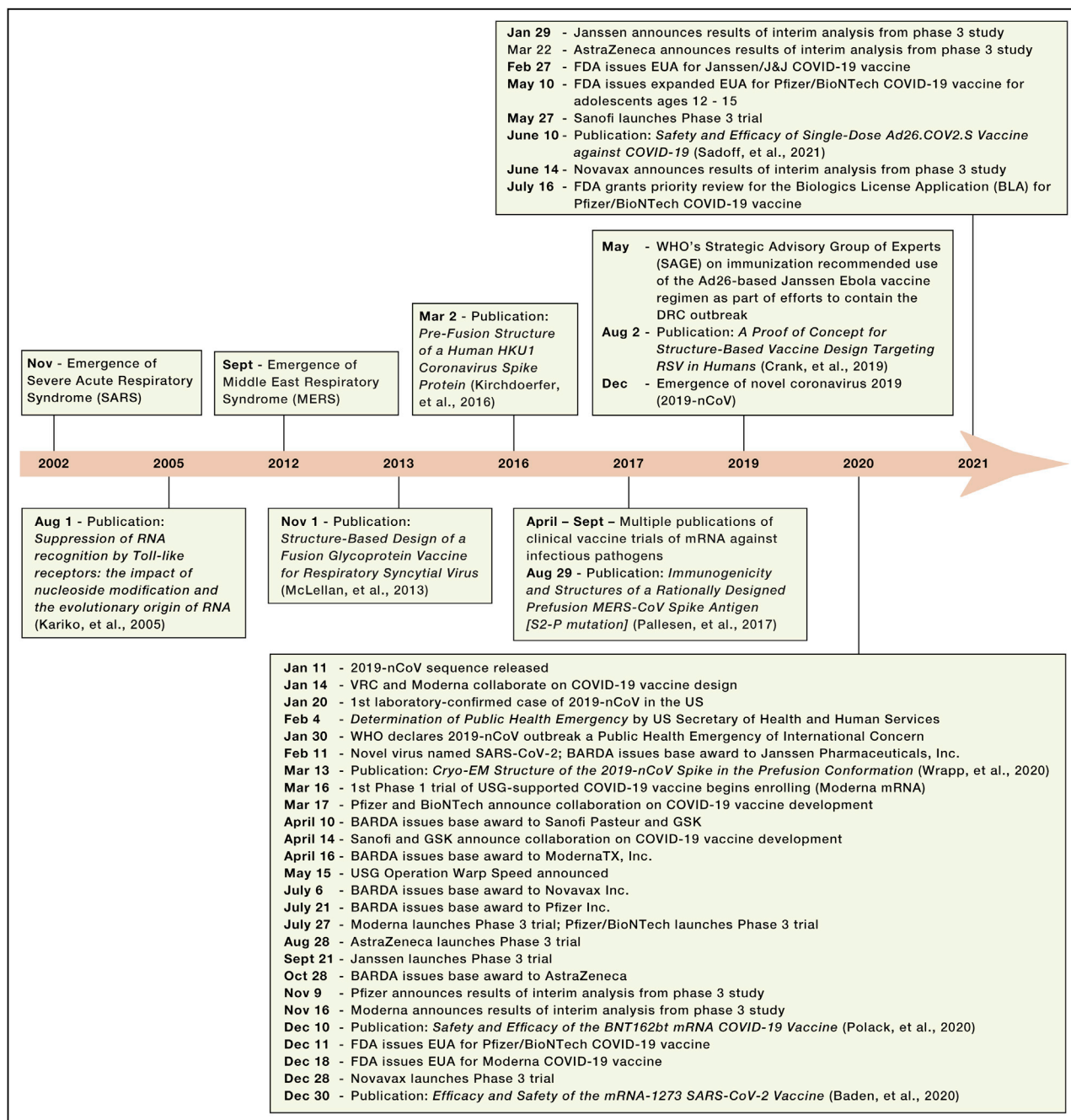
Jan 29 - Janssen announces results of interim analysis from phase 3 study
Mar 22 - AstraZeneca announces results of interim analysis from phase 3 study
Feb 27 - FDA issues EUA for Janssen/J&J COVID-19 vaccine
May 10 - FDA issues expanded EUA for Pfizer/BioNTech COVID-19 vaccine for adolescents ages 12 - 15
May 27 - Sanofi launches Phase 3 trial
June 10 - Publication: *Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against COVID-19* (Sadoff, et al., 2021)
June 14 - Novavax announces results of interim analysis from phase 3 study
July 16 - FDA grants priority review for the Biologics License Application (BLA) for Pfizer/BioNTech COVID-19 vaccine

May - WHO's Strategic Advisory Group of Experts (SAGE) on immunization recommended use of the Ad26-based Janssen Ebola vaccine regimen as part of efforts to contain the DRC outbreak
Aug 2 - Publication: *A Proof of Concept for Structure-Based Vaccine Design Targeting RSV in Humans* (Crank, et al., 2019)
Dec - Emergence of novel coronavirus 2019 (2019-nCoV)

Mar 2 - Publication: *Pre-Fusion Structure of a Human HKU1 Coronavirus Spike Protein* (Kirchdoerfer, et al., 2016)

Nov - Emergence of Severe Acute Respiratory Syndrome (SARS)

Sept - Emergence of Middle East Respiratory Syndrome (MERS)

| 2002 | 2005 | 2012 | 2013 | 2016 | 2017 | 2019 | 2020 | 2021 |

Aug 1 - Publication: *Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA* (Kariko, et al., 2005)

Nov 1 - Publication: *Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus* (McLellan, et al., 2013)

April – Sept – Multiple publications of clinical vaccine trials of mRNA against infectious pathogens
Aug 29 - Publication: *Immunogenicity and Structures of a Rationally Designed Prefusion MERS-CoV Spike Antigen [S2-P mutation]* (Pallesen, et al., 2017)

Jan 11 - 2019-nCoV sequence released
Jan 14 - VRC and Moderna collaborate on COVID-19 vaccine design
Jan 20 - 1st laboratory-confirmed case of 2019-nCoV in the US
Feb 4 - *Determination of Public Health Emergency* by US Secretary of Health and Human Services
Jan 30 - WHO declares 2019-nCoV outbreak a Public Health Emergency of International Concern
Feb 11 - Novel virus named SARS-CoV-2; BARDA issues base award to Janssen Pharmaceuticals, Inc.
Mar 13 - Publication: *Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation* (Wrapp, et al., 2020)
Mar 16 - 1st Phase 1 trial of USG-supported COVID-19 vaccine begins enrolling (Moderna mRNA)
Mar 17 - Pfizer and BioNTech announce collaboration on COVID-19 vaccine development
April 10 - BARDA issues base award to Sanofi Pasteur and GSK
April 14 - Sanofi and GSK announce collaboration on COVID-19 vaccine development
April 16 - BARDA issues base award to ModernaTX, Inc.
May 15 - USG Operation Warp Speed announced
July 6 - BARDA issues base award to Novavax Inc.
July 21 - BARDA issues base award to Pfizer Inc.
July 27 - Moderna launches Phase 3 trial; Pfizer/BioNTech launches Phase 3 trial
Aug 28 - AstraZeneca launches Phase 3 trial
Sept 21 - Janssen launches Phase 3 trial
Oct 28 - BARDA issues base award to AstraZeneca
Nov 9 - Pfizer announces results of interim analysis from phase 3 study
Nov 16 - Moderna announces results of interim analysis from phase 3 study
Dec 10 - Publication: *Safety and Efficacy of the BNT162bt mRNA COVID-19 Vaccine* (Polack, et al., 2020)
Dec 11 - FDA issues EUA for Pfizer/BioNTech COVID-19 vaccine
Dec 18 - FDA issues EUA for Moderna COVID-19 vaccine
Dec 28 - Novavax launches Phase 3 trial
Dec 30 - Publication: *Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine* (Baden, et al., 2020)

Figure 1. Milestones and events leading to the successful development of COVID-19 vaccines
Key events leading to the accelerated development of COVID-19 vaccines, including insights from previous research that contributed to the scientific rationale underlying vaccine design.

that defy traditional ways of designing and developing vaccines. Modern vaccinology takes advantage of advances in viral immunology, structural biology, and novel vaccine platforms that can safely elicit robust immunity. One major area of progress has been in the definition of the structures of viral surface proteins as well as a detailed understanding of how protective antibodies target these proteins. The research emanating from the studies of surface proteins of viruses, such as influenza, human immuno-

deficiency virus (HIV), and respiratory syncytial virus (RSV), has been invaluable to hone our understanding of how protein structure impacts immune recognition of complex surface proteins. A major aim of structure-based design is to hold the metastable viral surface protein in the native conformation recognized by potent neutralizing antibodies (Sanders and Moore, 2021). A key milestone in this area was the stabilization of the RSV fusion (F) surface protein (McLellan et al., 2013a, 2013b) that led to

improved immunogenicity in phase 1 clinical trials and to the advanced clinical testing of this and related candidate vaccines (Crank et al., 2019). The recognition of the importance of stabilizing viral surface proteins as immunogens led investigators to solve the atomic-level structure of the HKU1 betacoronavirus and subsequently to assess the impact of introducing stabilizing mutations into the spike protein of HKU1, SARS, and Middle East respiratory syndrome (MERS). These studies determined that altering two sequential amino acids to prolines in the central helix of the transmembrane portion of the protein could help stabilize the spike protein in its native conformation, increase protein expression, and improve immunogenicity (Pallesen et al., 2017). Once the sequence of the novel coronavirus became available on January 11, 2020, the sequence alignment allowed the two proline mutations to be introduced into what we now term the SARS-CoV-2 spike protein, and fortunately, this facilitated the rapid and successful design and production of a high-quality immunogenic spike protein that fueled the rapid development of diagnostics, therapeutics, and vaccines at the start of the COVID-19 pandemic.

Advances in vaccine platform technologies

Traditional vaccines reproduce the pathogen in some form, whether live-attenuated or inactivated or as a subunit of the pathogen delivered as a recombinant protein or protein particle as first done for hepatitis B (Gerberding and Haynes, 2021; Hilleman, 2000; McLean et al., 1984; Plotkin, 2009; Valenzuela et al., 1982). These vaccine modalities have worked extraordinarily well for many pathogens, including measles, polio, hepatitis B, and human papilloma virus (HPV), though important gaps remain for vaccine development (Gerberding and Haynes, 2021). New vaccine modalities include gene-based platforms that encode the antigen of interest in a manner that allows the body to produce the vaccine antigen. Gene-based technologies include nucleic-acid-based vaccines (DNA and mRNA) and viral vectors such as recombinant adenoviruses (rAds). The endogenous production of vaccine antigens from host cells partially mimics the immune response to natural infection and facilitates elicitation of CD4+ and CD8+ T cell responses as well as humoral immune responses. For COVID-19, both mRNA and rAd vectors have proven to induce effective immunity. Viral vectors such as the human rAd26 or the chimpanzee vector (ChAd) can be readily manipulated to express the gene of interest and are produced by a standardized manufacturing process, facilitating a rapid pathway to clinical evaluation. Likewise, a particular advantage of the mRNA platform is the rapidity with which candidate vaccines can be designed and produced. The synthetic chemical nature of mRNA vaccines and their lipid nanoparticle components circumvent the need to make a biological product grown in cell culture, thus simplifying production and shortening the time to the clinic (Pardi et al., 2018).

While gene-based platforms have been emphasized for their rapid capability, recombinant protein technologies, especially when combined with new powerful adjuvants, have several potentially advantageous features. Protein vaccines such as recombinant hepatitis B and the virus-like particle for HPV have been licensed for global use, have a strong history of safety and immunological data to reference, can be made at relatively low cost in large quantities, and can be used in various popula-

tions. Given the differing attributes of various vaccine platforms, the USG COVID response team thought it important to develop and test vaccines from more than one platform technology. *A priori*, it was not known which vaccine platforms could be effectively manufactured and advance rapidly into phase 3 trials. Further conjecture related to which platform would demonstrate an acceptable safety profile and produce protective immunity. This led to the decision to fund the development of three distinct platforms: mRNA, rAd, and subunit protein.

Scientific basis of SARS-CoV-2 vaccine development

Spike is the primary surface feature on coronavirus virions and is responsible for both attachment and entry into target cells, making it an important target for neutralizing antibodies (Liu et al., 2020; Wrapp et al., 2020). It is also large, with roughly twice as many amino acids as HIV Env or RSV F and known to contain multiple T cell epitopes (Mateus et al., 2020). Therefore, the spike glycoprotein is the vaccine target antigen of choice, and it can be delivered by several different modalities. For either protein-based or gene-based delivery of coronavirus (CoV) spike, a number of vaccine design choices need to be made about the spike construct that will determine its biophysical and antigenic properties, impact manufacturability, and ultimately potentially impact immunogenicity and vaccine efficacy. One choice is whether to include the entire spike protein with the surface ectodomain (S1) and the transmembrane domain (S2) or just the ectodomain (S1) or a subdomain of the ectodomain such as the receptor binding domain (RBD). The RBD is responsible for viral attachment via ACE2. Vaccines comprised of RBD can induce robust neutralizing activity, especially when measured in assays with high levels of the angiotensin-converting enzyme 2 (ACE2) receptor on target cells that may be biased for detection of antibodies blocking attachment (Cohen et al., 2021; Saunders et al., 2021). Antibodies to the N-terminal domain (NTD) or the transmembrane domain can also neutralize virus by interfering with protein rearrangement, resulting in fusion inhibition (Liu et al., 2020; McCallum et al., 2021). Therefore, using the entire spike ectodomain has the potential to induce a broader repertoire of antibody specificities, including those to quaternary epitopes that can neutralize by different mechanisms and theoretically be more resistant to immune escape. When expressed as a soluble protein, the spike trimer needs a C terminus trimerization domain to maintain its structure. On the other hand, the RBD is only about 1/6 the size of full-length spike and can be presented as a monomer, potentially improving the ease and cost of manufacturing, and can be displayed in a nanoparticle format.

Spike is a trimer of S1/S2 heterodimers, and the furin cleavage site (RRAR) between S1 and S2 is important for mediating the fusion process but not necessarily important for protein folding and assembling into the right conformation of the functional trimer. For protein-based vaccines, eliminating the cleavage site with an amino acid linker like GSAS results in a more uniform population of proteins. For spike antigens expressed from gene-based vectors, maintaining the transmembrane domain and keeping spike anchored in the cell membrane is more immunogenic than designing the antigen to be secreted from the cell, and current mRNA and viral-vector vaccines take this approach (Table 1). In the transmembrane context, the spike protein appears to be

Table 1. COVID-19 vaccine platforms, sponsors, and vaccine candidates

OWS COVID-19 vaccine candidates

Platform	Sponsor	Vaccine platform	Target protein	Dosing regimen	Furin cleavage site
Nucleic acid	Pfizer/BioNTech	mRNA	prefusion stabilized (S-2P) transmembrane anchored full-length spike protein	2 doses/21 days apart	native
	Moderna	mRNA	prefusion stabilized (S-2P) transmembrane anchored full-length spike protein	2 doses/28 days apart	native
Viral vector	AstraZeneca/Oxford	chimpanzee adenovirus vector	transmembrane anchored spike protein	2 doses/28 days apart	native
	Janssen	human adenovirus vector (26)	prefusion stabilized (S-2P) transmembrane anchored full-length spike protein	1 dose	mutated furin cleavage site R682S and R685G
Protein-based + adjuvant	Novavax	recombinant protein (insect cell) + matrix M adjuvant	prefusion stabilized (S-2P) full-length spike protein	2 doses/21 days apart	mutated furin cleavage site 682-RRAR-685 to 682-QQAQ-685
	Sanofi/GSK	recombinant protein (insect cell) +AS03 adjuvant	prefusion stabilized ectodomain (S-2P) spike protein with T4-foldon trimerization domain	2 doses/21 days apart	mutated furin cleavage site

Non-OWS COVID-19 vaccine candidates, examples

Platform	Sponsor	Vaccine platform	Target protein	Dosing regimen	Furin cleavage site
Nucleic acid	CureVac	mRNA	prefusion stabilized (S-2P) transmembrane-anchored spike protein	2 doses/28 days apart	intact S1/S2 cleavage site and transmembrane domain
Viral vector	Gamaleya National Research Centre for Epidemiology and Microbiology	human adenovirus vectors (rAd26 and rAd5)	full-length spike protein	rAd26 prime, rAd5 boost 21 days apart	–
Inactivated virus	Sinovac/China National Pharmaceutical Group	vero cell-based, β-propiolactone-inactivated vaccine based on the CZ02 strain; aluminium hydroxide-adjuvanted	whole virus	2 doses/14–28 days apart	–
	Sinopharm/Beijing Institute of Biological Products	vero cell-based, β-propiolactone-inactivated vaccine based on the 19nCOV-CDC-TAN-HB02 strain; aluminium hydroxide-adjuvanted		2 doses/21–28 days apart	–
	Covaxin/Bharat Biotech	whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule (IMDG) adsorbed to alum (Algel)		2 doses/28 days apart	–

COVID-19 vaccine platforms, sponsors, and vaccine candidates (Baden et al., 2021; Batty et al., 2021; Bos et al., 2020; ClinicalTrials.gov, 2021; Corbett et al., 2020; Folegatti et al., 2020; Goepfert et al., 2021; Jackson et al., 2020; Keech et al., 2020; Lee et al., 2021; Mercado et al., 2020; Polack et al., 2020; Sadoff et al., 2021; Tian et al., 2021; Walsh et al., 2020; Vogel et al., 2021) and examples of non-OWS COVID-19 vaccine platforms, sponsors, and vaccine candidates (Batty et al., 2021; Ella et al., 2021a, 2021b; Kremsner et al., 2020; Lee et al., 2021; Logunov et al., 2020; Rauch et al., 2021; Wang et al., 2020; WHO, 2021a, 2021b; Zhang et al., 2021). The Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, Novavax, and Sanofi/GSK vaccines are all based on the Wuhan-Hu-1 spike protein sequence. The Sanofi product will include both a monovalent protein (Wuhan-Hu-1) and a bivalent product (Wuhan-Hu-1 + protein based on the beta [B.1.351] sequence).

partially stabilized, and the furin cleavage site could be retained (e.g., Moderna, BioNTech/Pfizer mRNA, and AstraZeneca rAd vector) or be mutated (e.g., Janssen's rAd26 or the Novavax candidate).

There are numerous options for formulation and modality of vaccine antigen delivery, and a full discussion is beyond the scope of this general review. The vaccine tracker and landscape tables maintained by the World Health Organization (WHO) list

more than 280 COVID-19 vaccine candidates (WHO, 2021c), of which more than 100 have reached clinical evaluation and a few of the most advanced have been approved for emergency use listing (WHO, 2021d).

A new paradigm for rapid vaccine development

In early 2020, as the SARS-CoV-2 pandemic spread around the globe, a USG scientific enterprise, which would eventually be known as OWS, began developing a coordinated response strategy to the outbreak. Scientists from the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health (NIH), both part of the HHS, began to systematically evaluate over 70 potential SARS-CoV-2 candidate vaccines and vaccine technologies. Key evaluation criteria included robust preclinical data, experience with the vaccine platform, evaluation of the vaccine design and prediction of efficacy, dosing regimen, manufacturability, and anticipated safety profile.

During these initial efforts, senior USG officials from BARDA and NIH were planning a broad all-hands-on-deck approach to the preclinical and clinical development, manufacturing, and distribution of medical countermeasures to address the COVID-19 pandemic. This culminated in recommendations to the Office of the Assistant Secretary for Preparedness and Response (ASPR) and HHS leadership to form a comprehensive integrated response to this new pandemic pathogen and the formal announcement of OWS on May 15, 2020 (HHS, 2020; Slaoui and Hepburn, 2020). OWS was formed as an integrated program comprised of components of HHS, including ASPR, BARDA, NIH, and the Centers for Disease Control and Prevention (CDC), together with components of the Department of Defense (DoD), including both medical research and logistics capabilities. The OWS vaccine-development team down-selected leading candidate vaccines for advanced development.

The selections included vaccine platforms such as mRNA with the potential for rapid advancement to the clinic, viral vector platforms with substantial clinical history, and traditional adjuvanted protein-based vaccines. This strategy reflected the recognition that while speed of development was a key goal, there was uncertainty about which vaccine designs and platform technologies would meet the key criteria of safety and clinical efficacy, together with capacity for scaled-up manufacturing of millions of product doses. By choosing both new and traditional vaccine platforms and testing several vaccine designs, it was believed that the likelihood of achieving one or more successful products would be maximized. Importantly, the vaccine development efforts of OWS relied on partnerships with pharmaceutical and biotech companies who would be responsible for product manufacturing, advanced development, and licensure. The OWS-funded program did not include a traditional inactivated whole virus (IWV) vaccine approach, but IWV vaccines have been developed by other experienced vaccine-development teams, such as the Chinese national pharmaceuticals groups Sinovac and Sinopharm and India's Covaxin from Bharat Biotech. In addition, the Russian Gamaleya National Research Centre developed a rAd vaccine based on rAd26 prime and rAd5 boost, and CureVac is currently conducting a phase 3 trial for their mRNA candidate (Table 1). This perspective will focus on the advanced development of the USG-supported vaccines.

After selecting vaccine candidates for funding and advanced development, OWS scientists were confronted with fundamental operational decisions: (1) how to form public-private partnerships to safely accelerate the clinical development of these candidates, (2) how to efficiently design and conduct placebo-controlled efficacy trials, ensuring measurement of key endpoints and adherence to FDA guidance (FDA, 2020a) at clinical sites with active community transmission, and (3) how to facilitate management and oversight of simultaneous efficacy trials and ensure that OWS could effectively assess efficacy and immune correlates across multiple vaccine candidates. To accomplish these goals, while maintaining industry-sponsor control of the product and regulatory process, OWS established a paradigm for independent but harmonized phase 3 vaccine trials (Corey et al., 2020). Harmonized trials would be randomized placebo-controlled trials with closely aligned primary endpoints (e.g., prevention of symptomatic COVID-19) and powered to be able to establish a point estimate of vaccine efficacy (VE) of >50% with the lower bound of the 95% confidence interval (CI) above 30%, as indicated by FDA guidance. Further, study size was adjusted to obtain final analysis within 6 months. In addition, NIH established a common independent data safety and monitoring board (DSMB) staffed with expert clinicians and statisticians from government and academia to oversee the trials (Corey et al., 2020). OWS also began a process to establish a core set of validated assays to measure vaccine-induced binding and neutralizing antibody responses as well as a biostatistical group to evaluate the data (R. Koup, personal communication). Thus, each trial would have a common set of immune measurements from which to assess potential immune correlates of protection and to facilitate cross-protocol comparisons.

The independent harmonized-clinical-trial approach was favored over a master protocol with a common placebo for several reasons: (1) the phase 3 trials would not run concurrently, as each sponsor would potentially launch phase 3 efficacy trials on a timeline dictated by its product developmental timelines, (2) the required vaccine trials were large, requiring between 30,000–60,000 participants, and it was not feasible for OWS to manage all operational aspects of such trials with 3 to 5 arms of that size, and (3) in the setting of vaccine efficacy, the application for licensure or emergency use must be submitted by the pharmaceutical sponsor of the product (as defined by FDA regulations), and this is most efficient if the critical safety and clinical outcome data reside with the product sponsor who also holds the necessary manufacturing data for a given product. Thus, a key tenet of the OWS approach was that each company would be the regulatory sponsor responsible for the conduct of their own phase 3 trial but that the trial would be done in collaboration with OWS and NIH and overseen by the common DSMB. To meet the need for vast study enrollment, the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH, merged its existing Division of AIDS (DAIDS) and Division of Microbiology and Infectious Diseases (DMID) clinical research networks with additional DoD sites and some from the Veterans Affairs clinical network into a combined network called the COVID-19 Prevention Network (CoVPN; https://www.coronaviruspreventionnetwork.org). The CoVPN was made up of academic and hospital-based research sites that would enroll study volunteers along with contract research organization sites selected by each vaccine

sponsor. Thus, with the exception of the Pfizer trial, which was conducted by the company without OWS support, the conduct of each phase 3 trial was a close collaboration between the industry sponsor and the NIH and OWS teams.

To design and implement the phase 3 protocols and ensure enrollment of racially and ethnically diverse populations and those disproportionally affected by COVID-19, clinical research specialists from OWS worked side by side with clinical trial- and participant-recruitment experts from the CoVPN and each sponsor. Reporting providing real-time indicators and projected COVID-19 incidence was developed to inform decision making for site selection and prioritization. Materials included US-county-level demographics, cases, hospitalizations, testing rates, and deaths among other data points as well as the CDC case-forecasting ensemble model and extended time horizon epidemiological modeling tailored to prospective trial site selections from sponsors. To further support diverse participant enrollment, senior scientific leadership participated in community forums to raise awareness for study participation and utilized public and social media to engage communities (https://covid19community.nih.gov). In addition, the CoVPN and NIH launched a web-based participant-screening registry whereby individuals could self-report relevant household, social, and health status indicators in order to facilitate participant screening by trial site recruiters.

A key accelerator of vaccine deployment was the USG investment in commercial-scale manufacturing of candidate products from very early in the clinical development process—prior to the availability of phase 3 results. Commercial scale manufacturing is an intricate fastidious process, and this investment ensured that a successful vaccine efficacy trial could translate promptly into a public-health intervention. While generally successful, there have been challenges in the manufacturing of some vaccine products, including availability of reagents, analytical assessment of the product, and final fill/finish, which is the process of filling vials with vaccine and finishing the process of packaging the medicine for distribution. This suggests that optimization of emergency manufacturing capacity should be a part of future preparedness priorities.

Efficacy trials and study results

On July 27, 2020, just over 6 months after the first sequence of SARS-CoV-2 was released, both Moderna and Pfizer/BioNTech enrolled the first volunteers in their investigational COVID-19 efficacy trial studies (Figure 1). Moderna conducted their phase 3 study in 99 US clinical-trial sites and enrolled a diverse cohort of volunteers (Baden et al., 2021; Moderna, 2020a, 2020b). Pfizer/BioNTech conducted their phase 3 efficacy trial in 150 sites around the world, including those in the United States, Argentina, Brazil, South Africa, Germany, and Turkey (Pfizer, 2020a, 2020b; Polack et al., 2020). AstraZeneca launched a phase 3 efficacy trial, which included 88 clinical trial sites in the United States, Peru, and Chile, to evaluate their investigational COVID-19 vaccine product on August 31, 2020 (AstraZeneca, 2020, 2021). Janssen began enrollment in an international phase 3 trial of their Ad26.COV.S product in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States on September 21, 2020 (Janssen, 2021; Johnson & Johnson, 2020a; Sadoff et al., 2021). To evaluate their COVID-19 vaccine product, Novavax initiated an efficacy trial on December 28, 2020 with clinical

sites in the United States and Mexico (Novavax, 2020, 2021a, 2021b). On May 27, 2021, Sanofi, in partnership with GSK, launched a two-stage global efficacy trial (Sanofi, 2021). Stage one is currently evaluating their adjuvanted recombinant spike protein based on the ancestral (Wuhan-Hu-1) SARS-CoV-2 strain, and stage two will include a bivalent product that is a co-formulated mixture of the ancestral strain protein plus a protein based on the variant of concern (VOC) beta (B.1.351) strain.

As a testament to the remarkably effective conduct of these phase 3 trials and the unfortunate surge in COVID-19 infections in mid- to late 2020, the number of endpoints needed to establish vaccine efficacy accumulated over the course of less than 6 months. Hence, the first efficacy data emerged in November 2020 with the remarkable announcements by Pfizer and Moderna of 94%–95% efficacy in preventing symptomatic COVID-19 infection (Baden et al., 2021; Polack et al., 2020). Based on these efficacy results and a robust safety profile, Pfizer/BioNTech submitted an EUA application to the FDA on November 20, 2020, which was granted on December 11, 2020 (FDA, 2020c). On November 30, 2020, Moderna submitted an EUA request, which was issued by the FDA on December 18, 2020 (FDA, 2020b). On February 4, 2021, Janssen submitted a request for EUA, which was issued on February 27, 2021 (FDA, 2021b). While AstraZeneca and Novavax have yet to submit for EUA in the United States based on results from their pivotal efficacy trials, independently reviewed readouts provide indications of vaccine candidate efficacy (Table 2). In addition, the AstraZeneca vaccine has received authorization for use from multiple regulatory authorities, including the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). Enrollment in Sanofi's efficacy trial remains ongoing. An important aspect of the phase 3 data is the consistently high levels of efficacy against severe COVID-19 (Table 2). As an example, in the Moderna phase 3 dataset of 170 COVID-19 cases, 30 were severe—and all occurred in the placebo group. Importantly, the evaluation of vaccine efficacy has not ended with EUA submissions. At the time of full biologic license application (BLA), there will be many more COVID-19 cases from which to assess vaccine efficacy in real-world settings and to evaluate breakthrough cases by sequencing isolates to infer protection against variants circulating in study populations. In addition, the FDA requires continued monitoring of vaccine participants for a minimum of 2 years. Once efficacy is established, placebo recipients are offered vaccine and asked to remain in the study for follow up. This provides additional opportunities to assess the duration of protection in the context of these studies while continuing to monitor volunteer safety, albeit without the contemporaneous control group.

Of note, recently reported results of the CureVac mRNA vaccine encoding a transmembrane-anchored stabilized spike protein indicate a rather disappointing 47% efficacy against symptomatic COVID-19 (CureVac, 2021). This vaccine was reported to have relatively high levels of systemic reactogenicity despite a relatively low dose of 12 μg, as compared to Moderna (100 μg dose) and Pfizer-BioNTech (30 μg dose) (Jackson et al., 2020; Kremsner et al., 2020; Walsh et al., 2020). We do not know what accounts for this lower efficacy, but in addition to the lower dose, there may be differences in the modification of nucleotides, codon optimization of sequences, and other

Table 2. Randomized, placebo-controlled efficacy trial outcomes

Sponsor	Vaccine	Trial name	Dose/regimen	Trial launch	Number of volunteers	Case accrual	Distribution of cases (vaccine/ placebo)	Overall VE	Severe cases (vaccine/ placebo)	VE agaist severe disease	VE in older age groups	VE against SARS-CoV-2 variants		
												Alpha (B.1.1.7)	Beta (B.1.351)	Zeta (P.2)
Pfizer/ BioNTech	BNT162b2	C4591001	2 doses of 30 μg/21 days apart	July 27, 2020	43,548	170	8/162	95.0% (95% CI 90.3; 97.6)	1/4	75.0% (95% CI −152.6, 99.5)	94.7% (95% CI 66.7–99.9) (population ≥65)	–	100% (9 cases placebo group out of 800 trial participants)	–
Moderna	mRNA-1273	COVE Study	2 doses of 100 μg/28 days apart	July 27, 2020	30,420	196	11/185	94.1% (95% CI 89.3; 96.8)	0/30	100%	86.4% (95% CI 61.4; 95.5) (population ≥65)	–	–	–
Astra Zeneca	AZD1222	D8110 C00001	2 doses of 5×10^{10} viral particles/28 days apart	August 31, 2020	32,249	190	–	76% (95% CI 68; 82)	0/8	100%	85% (95% CI 58; 95) (population ≥65)	70·4%[a] (95% CI 43·6; 84·5)	10.4%[a] (95% CI − 76.8; 54.8)	–
Janssen	Ad26. COV2.S	ENSEMBLE	1 dose of 5×10^{10} viral particles	September 21, 2020	44,325	259	66/193	66.1% (95% CI 55.0; 74.8)	5/34	85.4% (95% CI 54.2; 96.9)	66.2% (95% CI 36.7; 83.0) (population >60)	–	64.0% (95% CI 41.2; 78.7) – 81.7% (95% CI 46.2; 95.4) (severe/critical)	68.1% (95% CI 48.8; 80.7) – 87.6% (95% CI 7.8; 99.7) (severe/ critical)
Novavax	NVX-CoV2372	PREVENT-19	2 doses of 5 μg SARS-CoV-2 rS adjuvanted with 50 μg Matrix-M1/21 days apart	December 28, 2020	29,960	77	1/63	90.4% (95% CI 82.9; 94.6)	0/4	100%	91.0% (95% CI 83.6; 95.0) (population >65, <65 with comorbidities; population with frequent COVID-19 exposure)	86.3%[a] (95% CI 71.3; 93.5)	51.0%[a] (95% CI −0.6; 76.2) (HIV-negative participants) 43.0%[a] (95% CI −9.8; 70.4) (combined HIV-negative and -positive population)	–

Randomized, placebo-controlled efficacy trial outcomes with point estimate and 95% CI shown as reported by Pfizer/BioNTech, Moderna, and Janssen in study result publications (Baden et al., 2021; Polack et al., 2020; Sadoff et al., 2021) and as announced by AstraZeneca and Novavax by press release (AstraZeneca, 2021; Novavax, 2021b). Dashes indicate unknown or undetermined as of yet.
[a]VE against SARS-CoV-2 variants demonstrated in additional phase 2, 2b, and 3 RCTs from individual sponsors (Emary et al., 2021; Heath et al., 2021; Madhi et al., 2021; Shinde et al., 2021).

characteristics of the mRNA formulation or the lipid nanoparticle used to encapsulate the mRNA (Dolgin, 2021).

Vaccine safety: The challenge of real-time safety surveillance at a massive scale

Because preventive vaccines are predominantly evaluated in healthy population cohorts and distributed among the general population, a high standard of safety is required. To meet this requirement, the CDC and FDA developed large comprehensive passive and active vaccine-safety surveillance systems, collecting reported outcomes as well as surveying hundreds of millions of healthcare or insurance records in a given period of time (Destefano et al., 2018). But the coronavirus pandemic posed an unusual new scenario, calling for real-time safety surveillance of potentially all US adults receiving a vaccine during a limited period of time. The CDC quickly adapted their proven post-licensure monitoring systems by creating a new post-authorization safety surveillance tool, V-safe (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html), designed and deployed specifically to actively follow vaccinated individuals, including pregnant populations who were also surveyed via a custom registry, in real time. Although safety is monitored throughout the development cycle and deployment of a vaccine, certain rare adverse events associated with immunizations (or any medication) can only be detected once millions of individuals have received the intervention. During the past year, it was reassuring to observe safety systems in action, detecting potential adverse event signals in real time, either during the evaluation phase or during deployment, and enabling health experts to quickly investigate and publicly discuss the probability of association with the individual vaccines authorized for emergency use. Safety checks were evident when Janssen was able to quickly institute a pause in dosing during their phase 3 trial after observing a serious adverse event and work with the DSMB and FDA to review data and resume the trial safely (Johnson & Johnson, 2020b). CDC safety systems also effectively contributed to the rapid benefit and risk analysis for rare adverse events, such as anaphylaxis and thrombosis-thrombocytopenia outcomes associated with mRNA and vector vaccines, respectively, and more recently, a possible association between mRNA vaccines with myocarditis in younger individuals. These immunization safety systems will continue to survey coronavirus vaccines, offering reassurance for the public for years to come. The ability to access data, analyze results, and issue recommendations based on scientific evidence in the midst of a crisis required unparalleled coordination and effort to ensure the public's trust. It is also important to highlight that incentivizing transparency to gain public trust was a priority during the entire USG-led operation. This was evident by the unprecedented public sharing, including publication of phase 3 efficacy trial protocols, release of EUA submission materials to be discussed at each FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, and open review of safety data at the CDC Advisory Committee on Immunization Practices (ACIP) meetings.

Real-world vaccine effectiveness and duration of protection

Once vaccines are authorized or licensed for use, real-world vaccine effectiveness (RWE) can be assessed using case control and observational studies. These inform how well the vaccines perform in broader populations after authorization, including in those with a wider range of underlying health conditions, greater age distribution, and in less-controlled clinical settings. RWE data are continuing to accumulate and have confirmed and augmented the randomized controlled trial results showing high efficacy against symptomatic COVID-19 and even higher efficacy against severe disease, hospitalization, and death (Figure 2; Table 3). Understanding the duration of vaccine efficacy beyond the initial 6 months of observation will require continued monitoring. As a potential surrogate of vaccine effectiveness, the level of vaccine-induced antibodies among volunteers from the initial phase 1 clinical trials conducted over a year ago have been monitored. Recent studies show that vaccinated individuals maintain detectable levels of neutralizing antibodies for at least 6 months after immunization when measured against the prototype SARS-CoV-2 strain (Barouch et al., 2021; Widge et al., 2021). However, when measured against antigenically divergent VOCs, such as beta or delta, the serum neutralization titers of individuals decrease to varying degrees, as discussed below, and may be less durable (Moriyama et al., 2021; Pegu et al., 2021). These data do not necessarily indicate that vaccine-mediated protection will be lost against some VOCs, as a brisk anamnestic response can still confer clinical protection, particularly against severe disease. However, it will be important to continue to monitor the duration of vaccine-induced immune responses and pair this analysis with what is learned from correlates of protection (CoP) analysis. Most importantly, we need continued clinical monitoring of those vaccinated to assess duration and level of protection, including in populations such as the elderly or those on immune-modulating medications who may respond less vigorously to vaccination. Such clinical data can be augmented by sequence-based surveillance of vaccine breakthrough infections.

Vaccine effectiveness and variants of concern

As expected for a single-stranded RNA virus, random mutations occur over time throughout the SARS-CoV-2 genome (Callaway, 2020). As the COVID-19 pandemic continues, mutations resulting in advantageous amino-acid substitutions are accumulating and can impact the efficiency of viral spread and can facilitate immune escape. Such VOCs have arisen and spread with remarkable speed—likely driven by the large number of worldwide infections due to sustained transmission and in some cases by SARS-CoV-2 selection during prolonged viral replication and shedding in immunocompromised individuals (Karim et al., 2021; Tegally et al., 2021). In particular, antigenic variation of the spike protein can result in reduced recognition by neutralizing antibodies generated by natural infection or vaccination (Krause et al., 2021; Mascola et al., 2021; Walensky et al., 2021). As an example, vaccine-induced neutralizing antibody titers against the most antigenically diverse VOC beta are often 5- to 8-fold lower than against the original strain of SARS-CoV-2 (Choi et al., 2021; Jongeneelen et al., 2021; Liu et al., 2021; Pegu et al., 2021). This has raised concern that current vaccines based on the prototype isolate of SARS-CoV-2 may be less effective against some VOCs. Fortunately, both phase 3 data and emerging RWE data are, so far, reassuring (Table 3). Vaccine efficacy—for protection against both symptomatic and severe
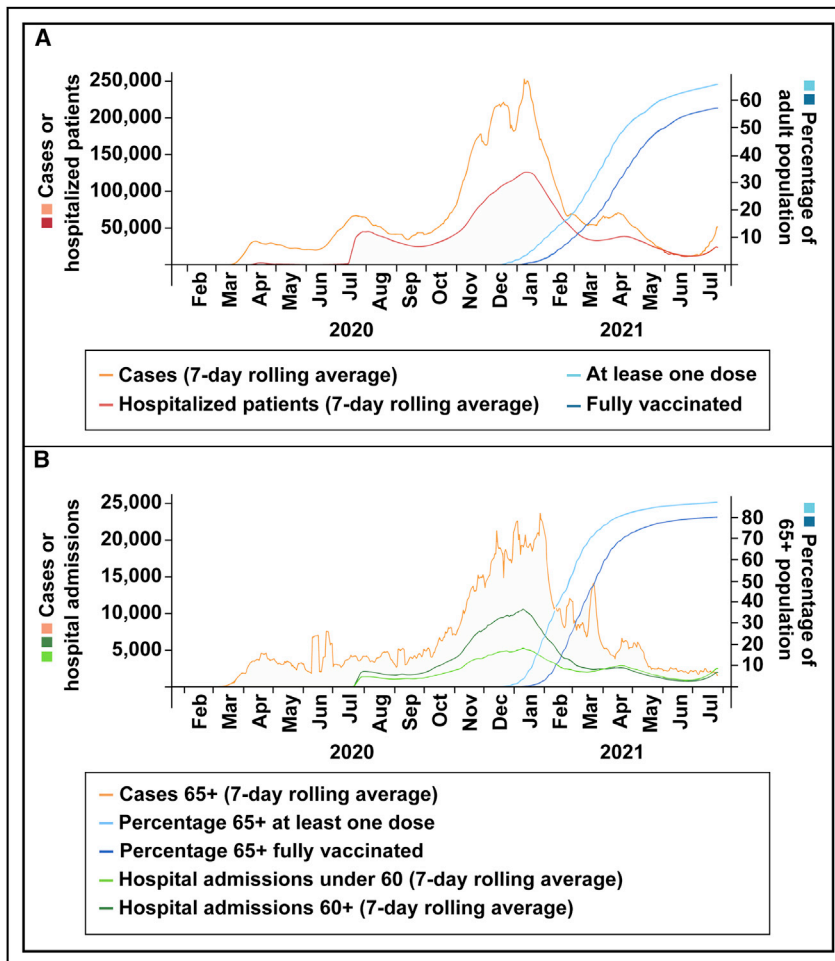
Figure 2. Graphical timeline of COVID-19 cases and hospitalizations and percentage of population receiving vaccine
(A) Adult population age 18 and over.
(B) Age-specific reported cases (age ≥65), hospital admissions (>60 and <60), and percentage of population vaccinated (≥65). Source: Aggregate metrics sourced from HHS Protect. Jurisdictions not reporting age-specific vaccine administration information omitted from population percentages. Totals may not represent full values.

mRNA-1273 vaccine in adolescents (Moderna, 2021), submitted an EUA request for adolescent designation on June 10, 2021. Pediatric cohorts are currently being enrolled in dose-finding, age-deescalating studies, which are closely monitored for reactogenicity and safety signals and are expected to be authorized by year's end.

Vaccination is recommended during pregnancy not only to protect the newborn during the first months of life via active placental transfer of antibodies, but also to protect the mother (and the fetus) from life-threatening outcomes if infection occurs during pregnancy (Allotey et al., 2020). The CDC ACIP recommended that pregnant women receive a SARS-CoV-2 vaccine in consultation with their provider (CDC, 2021a) based on a number of factors, including data demonstrating the increased risk of severe COVID-19 disease for pregnant women as compared to their non-pregnant counterparts (Villar et al., 2021; Zambrano et al., 2020). Additionally, the CDC established new surveillance tools, registries, and studies to closely follow and study pregnant and lactating women receiving COVID-19 vaccines (Collier et al., 2021; Shimabukuro et al., 2021). With data rapidly accumulating and observational prospective studies enrolling tens of thousands of pregnant women choosing to be vaccinated (Gray et al., 2021), it is unlikely that formal placebo-controlled studies will be conducted with EUA vaccines because of the considerable body of evidence demonstrating safety and efficacy of vaccination while pregnant.

Studies to understand the impact of COVID-19 vaccination in immunocompromised patients are underway, and initial results suggest variable responses, depending on the specific population (Boyarsky et al., 2021; Haidar et al., 2021; Monin et al., 2021; Werbel et al., 2021). Additional studies will enroll patients with specific conditions, such as rheumatologic disorders, cancers, organ transplantation, and immunosuppressive treatment. These studies aim to characterize the safety and immune response to vaccines in individuals with different levels and characteristics of immune suppression, as well as testing modified vaccination schedules that will inform the steps needed to protect these patients against severe disease. While most immunocompromised individuals were ineligible for the phase 3 efficacy

disease—remains high, including against VOCs (Table 3). It is important to note, however, that maintaining high levels of neutralizing antibodies against all circulating variants is most likely necessary to promote protection in the upper respiratory tract and also minimize viral transmission (Corbett et al., 2021). As the delta variant is becoming dominant in many parts of the world, it will be essential to monitor vaccine effectiveness against this variant. Fortunately, based on serum neutralization data, current vaccines appear to induce higher levels of neutralizing antibodies against this variant as compared to the beta variant (Choi et al., 2021; Jongeneelen et al., 2021).

Special populations: Children, pregnant women, and immune-compromised individuals
As phase 3 studies proceeded, US-funded manufacturers and agencies have systematically addressed the safety and immunogenicity of vaccines in special populations, including younger age groups; pregnant and lactating women; immunocompromised subjects; and those with autoimmune disease, asthma, and other conditions that may affect vaccine efficacy or disease severity. Pfizer recently amended their indication for EUA to immunize adolescent populations ages 12–15 (FDA, 2021a). Moderna, having demonstrated efficacy, safety, and immunogenicity for their

Table 3. Real world vaccine effectiveness data

Sponsor	Real-world vaccine effectiveness against prototype SARS-CoV-2 strain	Real-world vaccine effectiveness against SARS-CoV-2 variants							
		Alpha (B.1.1.7)		Beta (B.1.351)		Gamma (P.1)		Delta (B.1.617.2)	
		I/SI	SD	I/SI	SD	I/SI	SD	I/SI	SD
Pfizer/BioNTech	64%–99%	65%–100%	84%–100%	75%–88%	95%–100%	79%–88%	95%–100%	79%–88%	96%
Moderna	68%–99%	79%–100%	90%–96%	88%–96%	96%–100%	79%–88%	100%	–	–
AstraZeneca	–	66%–100%	86%–92%	–	–	–	–	60%–61%	92%
Janssen	77%	–	–	–	–	–	–	–	–

Real-world vaccine effectiveness (RWE) as assessed by case-control and observational studies of authorized two-dose regimens for Pfizer/BioNTech, Moderna, and AstraZeneca products (Abu-Raddad et al., 2021; Andrejko et al., 2021; Angel et al., 2021; Aran, 2021; Bahl et al., 2021; Bernal et al., 2021; Björk et al., 2021; Butt et al., 2021; Cavanaugh et al., 2021; CDC, 2021b; Chemaitelly et al., 2021; Chodick et al., 2021; Chung et al., 2021; Corchado-Garcia et al., 2021; Dagan et al., 2021; Fabiani et al., 2021; Goldberg et al., 2021; Haas et al., 2021; Hall et al., 2021; Lopez Bernal et al., 2021; Lumley et al., 2021; Martínez-Baz et al., 2021; Menni et al., 2021; Moustsen-Helms et al., 2021; Nasreen et al., 2021; Pawlowski et al., 2021; PHE, 2021; Pilishvili et al., 2021; Pritchard et al., 2021; Regev-Yochay et al., 2021; Sheikh et al., 2021; Stowe et al., 2021; Swift et al., 2021; Tande et al., 2021; Tang et al., 2021; Tenforde et al., 2021a, 2021b; Thompson et al., 2021a, 2021b; Vahidy et al., 2021; Vasileiou et al., 2021; Yassi et al., 2021; Young-Xu et al., 2021; Zacay et al., 2021) and 1-dose for Janssen (Corchado-Garcia et al., 2021). Value ranges for SARS-CoV-2 variants include vaccine effectiveness against infection/symptomatic infection (I/SI) and severe disease (SD), including hospitalization and death. Dashes indicate unknown or undetermined as of yet.

studies, people living with HIV (PLWH) who are well controlled on stable treatment were included. Ultimately, the numbers of PLWH in each study were too small to comprehensively determine efficacy.

Pandemic preparedness—Successes, gaps, and lessons learned

The United States is slowly emerging from a devastating public-health crisis (Cutler and Summers, 2020). While this infectious disease outbreak has contributed to improving our understanding of immunity, virus biology and accelerated pathways to first-in-human studies, gaps in diagnostic and manufacturing capacity and in designing medical countermeasures with distribution and access goals in mind, and the need for pre-established inter-agency systems to coordinate the response to pandemic threats have become evident. The key lessons from the SARS-CoV-2 pandemic need to be captured and used to inform how we can systematically prepare for future as-of-yet-unrecognized infectious disease pathogens (pathogen X). Having authorized vaccines available for widespread immunization less than a year after a novel virus was identified was possible, in this case, due to more than a decade of basic research, planning, and preparation for a betacoronavirus emergence motivated by the episodes of SARS-CoV-1 and MERS-CoV (Graham, 2020). Scientists and public-health officials now need to answer two key questions: (1) what else could have been done in anticipation or during the course of this pandemic to have immunized the population more rapidly, and (2) what would be needed to be fully prepared against pathogen X that may arise from one of the other 25 viral families (other than Coronaviridae) known to infect humans? This would require a comprehensive pandemic preparedness plan implemented across government agencies and academic institutions, and in collaboration with pharmaceutical partners, to proactively manage emerging viral threats. This includes the implementation or expansion of global surveillance and identification of new viruses; basic and translational research to establish

the knowledge and reagents needed for rapid response; early-stage product development for select prototypic viral pathogens; continuous support of a strong international clinical-trial infrastructure and deployment capacity; pre-established agreements and alignment between international regulatory agencies; and pre-existing public-private partnerships, academic collaborations, and government accords to manage the cooperation and communication needed for an effective global response (Graham and Corbett, 2020).

The events of the last 18 months have highlighted the importance of proactive pandemic preparedness and the capability for rapid response and have helped clarify the different types of activities and competencies needed for both. Preparedness requires a long-term investment in basic research and knowledge accumulation for pathogens of concern. For viruses, this would mean generating detailed information on structural biology of key antigenic targets, protein engineering for antigen design, pathogenesis, animal-model development, mechanisms of immunity, generation of reagents, and early-phase clinical evaluation for prototypes from each of the viral families or genera. Ideally this would include advancing some products through phases 1 and 2 and having some vaccine and monoclonal antibody prototypes on-the-shelf ready for efficacy testing in future outbreaks (Graham and Sullivan, 2018). For entirely new pathogens, a rapid pandemic response would mean having a generalizable vaccine design strategy for eliciting optimal B and T cell responses, including knowledge of neutralizing antibody epitopes based on the prototypic viruses with shared phenotypic properties. Another element of pandemic-response readiness, beyond having interventional products maintained in a stockpile and knowledge for rapid design, is to have the physical infrastructure and clinical networks available to conduct advanced clinical testing. The surge capacity for response could be in part derived from the complementary activities needed for preparedness. Sites that utilize molecular tools for surveillance could become centers for assay and diagnostics development.

The basic and translational research activities of preparedness could be turned to the preclinical research needed for product development and response. Prospective cohorts and networks established for serosurveys and routine development programs could pivot to be clinical-trial sites for testing new medical countermeasures (MCMs).

The complex operational and logistical aspects of delivering preventive vaccines and therapeutic agents have been revealed by COVID-19. Establishing supply chains for nucleotides, lipids, cell-culture media, vials, syringes, and many other necessities has been challenging. The difficulty of maintaining cold chains and equitable distribution of products to rural or low-income or historically disenfranchised populations and many other elements of managing a pandemic have been brought to the fore this year. We have also learned that pandemic response requires a global view. Applying solutions predominantly in high-income countries (HICs) during a pandemic will not control worldwide transmission or stop the emergence of variants elsewhere that may escape otherwise effective MCMs. Instead, there should be a coordinated global effort to solve regional problems before they become pandemic threats. This will require a new way of organizing and managing global resources and would be facilitated by establishing technical expertise and manufacturing capacity in low- and middle-income countries (LMICs). Ideally, we should improve and expand on the many successful examples of collaboration aiming to solve international infectious-disease crises. Such was the case with recent Ebola virus outbreaks, which culminated in the approval of both preventive and therapeutic MCMs made possible by closely collaborating with scientific experts from affected countries. There is clearly mutual benefit for HICs to support the distribution of resources for surveillance, product development, and manufacturing. Limited resources have been directed to this type of approach in the past, in part because developing MCMs for problems restricted to LMICs may not have immediate commercial value. However, after losing tens of trillions of dollars from the global economy during the last 1.5 years, the cost-benefit analysis for spending a few billion dollars a year on basic research for pandemic preparedness and for extending the research and development capacity of LMICs for improved pandemic response has changed.

Fortunately, the advent of new nimbler platform technologies such as mRNA and rAd have not only been highly effective, but also made it possible to accelerate manufacturing timelines of clinical grade vaccines and are compatible with regional manufacturing. These features can streamline commercial manufacturing and deployment of MCMs and may be suitable for establishing manufacturing sites in LMICs to address regional diseases. For the United States, there is the opportunity to strengthen our national emergency response via sustained funding for pandemic preparedness and increasing national manufacturing and fill-finish capacity while providing necessary funding to US agencies that support advanced development of MCMs, including facilitating advanced market commitments. In parallel, it is incumbent on the United States and other HICs to learn from the successes and remaining challenges of the ongoing pandemic and recognize the opportunity to extend research and development capacity to LMICs and establish the global agreements and coordination needed to solve regional problems before they become pandemic threats.

Concluding remarks

The sudden emergence of a previously unknown, highly contagious respiratory pathogen as the cause of a global pandemic necessitated the rapid development and testing of vaccines. This effort benefited from more than a decade of advances in vaccine antigen design and new vaccine platform technologies. The rapid development and high protective efficacy of these initial COVID-19 vaccines was not based on chance. This success was driven both by strategic investments in new vaccine technologies and by advances in immunogen design, such as the stabilizing of class I viral fusion proteins in their prefusion conformation. For COVID-19, this structure-based vaccine design resulted in levels of neutralizing antibodies that can surpass levels generated by natural COVID-19 infection. In retrospect, the road to success highlights the importance of investing in basic virology and vaccinology research and leveraging the prototype pathogen approach, having access to nimble manufacturing platforms ready for mass-scale use, and being able to rapidly design and launch pivotal efficacy studies with experienced trialists. The United States and international public-health experts now need to analyze lessons learned and insist on global agreements and commitment to pandemic preparedness, thereby increasing capacity for pandemic response, including the transfer of technology and manufacturing capability to LMICs, and intensifying surveillance efforts to identify potential pathogens and prevent or control future zoonotic spillover.

DECLARATION OF INTERESTS

B.G. is listed as an inventor of the following patent and patent application: WO/2018/081318 Prefusion Coronavirus Spike Proteins and their use; PCT Patent Application No. PCT/US2021/017709, filed on February 11, 2021, entitled "SARS-CoV-2 VACCINE." J.M. and B.G. are listed as inventors on the following patent application: U.S. Provisional Patent Application No. 63/140,250, filed on January 21, 2021, entitled "NEWCASTLE DISEASE VIRUS-LIKE PARTICLE DISPLAYING PREFUSION-STABILIZED SARS-COV-2 SPIKE AND ITS USE."

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