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HERE AND NOW: CLINICAL PRACTICE

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What Gastroenterologists Should Know About COVID-19 Vaccines

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In late December of 2019, cases of pneumonia caused by betacoronavirus SARS-CoV-2, closely related to SARS-CoV, were reported in the city of Wuhan, China. SARS-CoV-2 has resulted in a worldwide pandemic that continues to surge throughout the United States. Two vaccines for SARS-CoV-2 (the virus that causes COVID-19) are now available under emergency use authorization (EUA). An EUA was issued for the Pfizer-BioNTech COVID-19 vaccine on December 11, 2020, and another EUA was issued for the Moderna COVID-19 vaccine on December 18, 2020. Development of a coronavirus vaccine is not new. Vaccines against SARS-CoV were developed and tested in phase I trials in the 2000s, but development halted because of the disappearance of the virus.[1] Similarly, vaccines against Middle Eastern respiratory syndrome are under active development, but not at an accelerated pace, because of extremely low prevalence of the virus. The information gained from preclinical studies with SARS-CoV and Middle Eastern respiratory syndrome laid the groundwork to identify the spike protein as a target for development of a vaccine against SARS-CoV-2 at an early stage.[1]

Current COVID-19 Vaccine Development

In response to the pandemic, vaccine development has moved expeditiously with more than 200 COVID-19 vaccine candidates currently under development or in clinical trials.[2] These candidate vaccines are based on traditional approaches (inactivated or live attenuated vaccines), methods that have resulted in newly licensed vaccines (recombinant protein vaccine and vectored vaccines), and methods that have not resulted in a licensed vaccine (RNA and DNA vaccines).[1] Vectored vaccines incorporate 1 or more viral genes into the genome of viral vectors. These vectors are used to transport genetic material to host cells for transcription and expression of the desired coronavirus antigen.[1]

The Pfizer-BioNTech and Moderna vaccines use mRNA platforms. Preliminarily, these vaccines are reported to be more than 90% efficacious at prevention of symptomatic infections.[3] The vaccine antigen is coded by mRNA, which is protected by a lipoprotein coat. On vaccine administration, cells pick up the mRNA and translate it into a protein (in this case, the SARS-CoV-2 spike protein). The immune system then mounts a response to that protein. Although no mRNA vaccines against other infectious agents are presently available, mRNA vaccines have shown great promise, and in recent years many are in development to treat cancer and other infectious disease, such as Zika virus and cytomegalovirus.[1]

COVID-19 Vaccine Hesitancy

Widespread public acceptance and uptake of COVID-19 vaccines, in addition to concomitant prevention strategies, will be imperative in containing the spread of disease. Unfortunately, the general public's confidence in a COVID-19 vaccine under the US government's Operation Warp Speed (OWS) initiative has been clouded in an environment of political polarization and general mistrust of public health and governmental agencies. One survey found that having a vaccine available under a Food and Drug Administration (FDA) EUA was associated with a lower probability of willingness to get vaccinated, compared with standard FDA licensure.[4]

Vaccine hesitancy in adults is a complex issue and in general, there are few strategies to ameliorate this. Increasing uptake of vaccines is important, especially in

Abbreviations used in this paper: ACIP, Advisory Committee on Immunization Practices; EUA, emergency use authorization; FDA, Food and Drug Administration; OWS, Operation Warp Speed.

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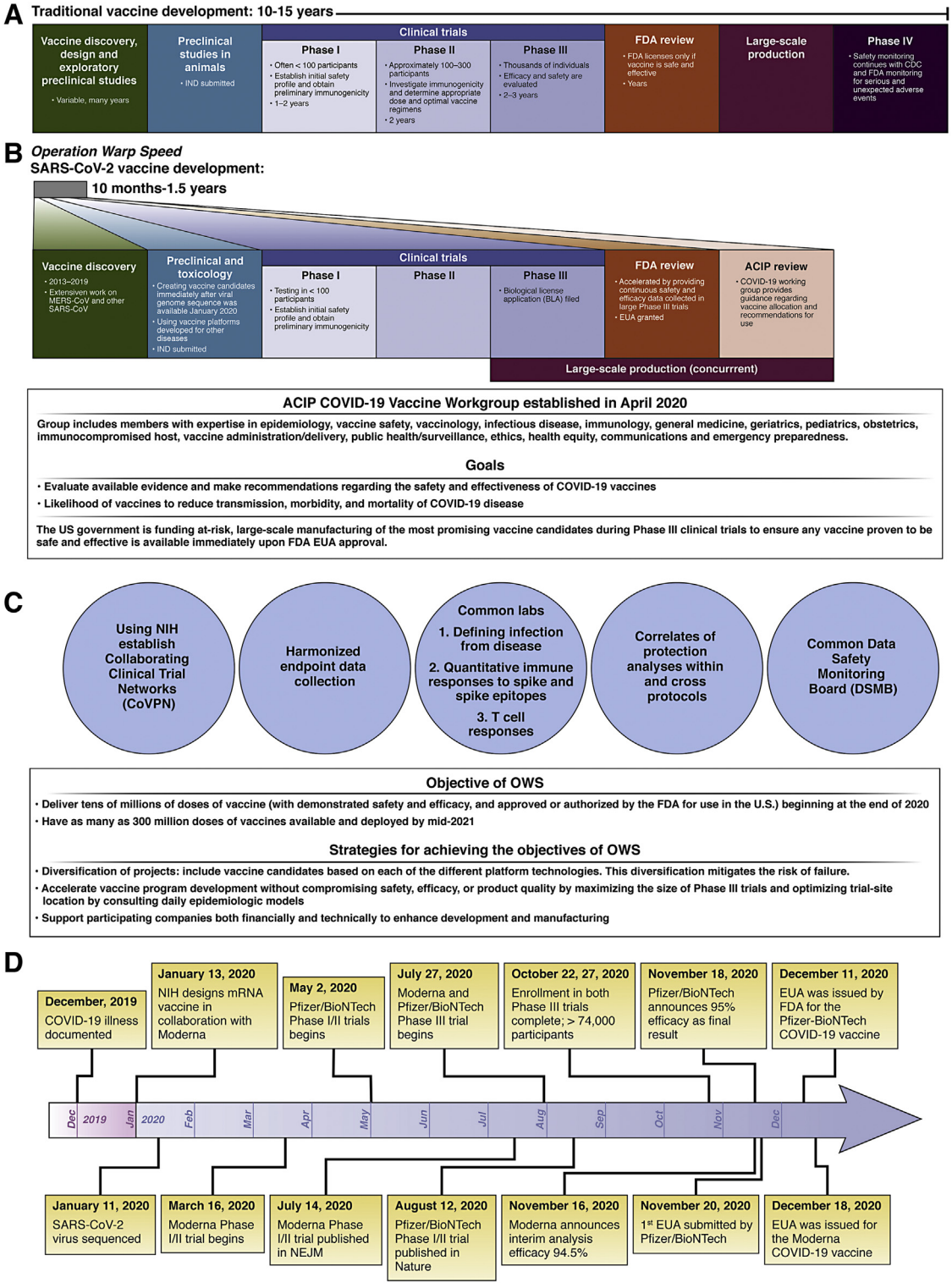

Figure 1. Overview of the typical vaccine development process and the accelerated development of a COVID-19 vaccines and the role of Operation Ward Speed. CDC, Centers for Disease Control and Prevention; NEJM, *New England Journal of Medicine*; NIH, National Institutes of Health.

the case of this pandemic, to achieve herd immunity and protect the general population. The Centers for Disease Control and Prevention's Vaccinate with Confidence campaign's strategic framework has been customized to increase support for COVID-19 vaccinations.[4] This campaign centers around the principles of reinforcing trust using transparent communication about the process of licensing, and safety of, vaccines; empowering health care providers to discuss vaccines with their patients by providing simple talking points; and engaging communities and individuals to explore service delivery strategies for vaccine distribution.[5]

Table 1. Vaccines in Parallel, Double-Blind, Placebo-Controlled, Efficacy Phase III Randomized Clinical Trials in the United States

Vaccine type	Manufacturer	Trial participants	Randomization ratio/IM doses	Primary outcome	Secondary outcomes
mRNA	Moderna	30,000 participants, ages 18+	1:1/2	Incidence of COVID-19 cases Participants with solicited local and systemic adverse reactions	Immunogenicity of vaccine
mRNA	BioNTech-Pfizer	43,998 participants ages 12+	1:1/2	Incidence of COVID-19 cases Incidence of adverse events and serious adverse events	Immunogenicity of vaccine
Nonreplicating viral vector	AstraZeneca	40,051 participants ages 18+	2:1/2	Incidence of COVID-19 cases Incidence of adverse events, serious adverse events, medically attended adverse events, adverse events of special interest Solicited local and systemic adverse reactions	Immunogenicity of vaccine
Nonreplicating viral vector	Jansen	60,000 participants ages 18+	1:1/1	Incidence of moderate to severe/ critical COVID-19 cases	Serologic conversion Immunogenicity of vaccine

How Have COVID19 Vaccines Been Developed, How Will They Receive EUA/Approval

Multiple vaccines for COVID-19 are being developed and tested on an unprecedented timeline. There are more than 200 vaccine candidates currently in development against SARS-CoV-2, and there are several candidate vaccines in the United States that are in active phase III clinical trials.[2] An overview of the typical timeline for vaccine development is illustrated in Figure 1.[6] Vaccine development is a complex, expensive, and lengthy process, with the typical timeline from preclinical studies to final licensure often ranging between 10 and 15 years.[7] The general public has voiced anxiety over the expedited timeline for vaccine development under OWS, with concern that there is not strict adherence to the regulatory standards for approval.[8] OWS, announced on May 15, 2020, is an initiative to control the COVID-19 pandemic by advancing the development, manufacturing, and distribution of vaccines, therapeutics, and diagnostics. OWS is a partnership of the Department of Health and Human Services, the Department of Defense, and the private sector. These agencies are providing funding and coordinated government support to accelerate vaccine development while still maintaining standards for safety and efficacy. OWS has worked with vaccine developers to enable, accelerate, and harmonize vaccine protocols of highly powered efficacy trials (Figure 1). Rather than eliminating steps from the traditional vaccine development timeline, trial phases are being combined and are proceeding simultaneously to expedite development.[6]

Although vaccine development has been accelerated, no steps in the typical vaccine development process have been skipped. Leadership of the FDA have emphasized that candidate vaccines are being reviewed according to their rigorous established legal and regulatory standards.[9] Vaccine efficacy and safety have been promising in several candidates to date. The primary end point for all vaccines currently in phase III clinical trials is COVID-19 symptomatic disease, as illustrated in Table 1.

The Advisory Committee on Immunization Practices (ACIP) has provided interim recommendations for the currently available COVID-19 vaccines, as outlined in Table 2.[10] These considerations are specific to the Pfizer and Moderna mRNA vaccines, which are available for use under EUA. An EUA differs from vaccine licensure. An EUA allows use of unapproved medical products to diagnose, treat, or prevent serious or life-threatening diseases or conditions in response to a declared public health emergency for which there are no adequate, approved, and available alternatives. The issuance of an EUA requires a determination by the FDA that the vaccine's benefits outweigh its risks based on data from at least 1 well-designed phase III clinical trial that demonstrates the vaccine's safety and efficacy in a compelling manner. The FDA expects manufacturers who receive an EUA to continue their studies to obtain comprehensive safety and effectiveness information and pursue final licensure of their product.[11,12] An EUA still requires review of extensive safety and efficacy data from phases I

Table 2. Interim Recommendations for Use of mRNA COVID-19 Vaccines

	Moderna	Pfizer
Authorized ages	≥18 y	≥16 y
Administration	Two doses administered intramuscularly: 100 μg, 0.5 mL; 28 d apart	Two doses administered intramuscularly: 30 μg, 0.3 mL each; 21 d apart
Interchangeability	COVID-19 vaccine are not interchangeable	
Coadministration with other vaccines	Should be administered alone, with a minimum interval of 14 d before or after administration with any other vaccine given the lack of data	
Immunocompromised persons (eg, patients with inflammatory bowel disease or chronic liver disease)	They should receive vaccine[a]	
Vaccination of persons with SARS-CoV-2 infection or exposure	Offered to persons regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection Persons with known current SARS-CoV-2 infection should be deferred[b]	
Vaccination of pregnant individuals[c]	Pregnant people who are part of a group recommended to receive the vaccine (eg, health care personnel) may choose to be vaccinated; a conversation of the risks and benefits of this vaccination with a health care provider is recommended, although not required	
Vaccination of lactating individuals[d]	A lactating person may choose to be vaccinated	
Precautions	History of severe allergic reaction to any other vaccine or injectable therapy[e]	
Contraindications	Severe allergic reaction to any component of the vaccine[f]	

[a]These populations should be counseled about the unknown vaccine safety profile and effectiveness in immunocompromised populations, and the potential for reduced immune responses.
[b]Vaccination should be deferred until the person has recovered from acute illness (if symptomatic) and criteria have been met to discontinue isolation.
[c]Limited data on the safety of the vaccine in pregnant people. Routine pregnancy testing is not required before receipt of the vaccine, and those who are trying to become pregnant do not need to avoid pregnancy after vaccination. There were no safety concerns with the Moderna vaccine demonstrated in rats in terms of female reproduction, development, or postnatal development.
[d]There are no data on the safety of the vaccine in lactating people. The vaccine is not thought to be a risk to the breast-feeding infant.
[e]No precautions necessary for dose with history of food, pet, insect venom, environmental, latex, or other allergies not related to vaccines or injectable therapies.
[f]Pfizer-BioNTech COVID-19 vaccine ingredients: 1,2-distearoyl-sn-glycero-3-phosphocholine, 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, cholesterol, (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose. Moderna COVID-19 ingredients: polyethylene glycol 2000 dimyristoyl, 1,2-distearoyl-sn-glycero-3-phosphocholine, cholesterol, SM-102 (proprietary to Moderna), tromethaminelycerol, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

and II of vaccine studies, with an expectation that phase III data include a median follow-up of at least 2 months for vaccine recipients. This 2-month timeframe was selected because adverse events considered potentially linked to vaccination typically start within 6 weeks of vaccine receipt.[11] Vaccines made available with EUA will have met this safety requirement. Furthermore, long-term safety data will continue to be collected for those in clinical trials and those who receive the vaccine under an EUA with safety monitoring systems, such as Vaccine Adverse Event Reporting System, the Vaccine Safety Datalink, and Clinical Immunization Safety Assessment and safety review by the Institute of Medicine.[13]

Role of the US Advisory Committee on Immunization Practice

The FDA has indicated that any decision about vaccine EUA or licensures will be discussed by the ACIP.[9] The ACIP is a group that provides advice to the Centers for Disease Control and Prevention Director and the Secretary of the Department of Health and Human Services. Because of their standing as a federal advisory committee, they hold open meetings with public involvement, and report their recommendations transparently. In addition to the 15 voting members, the committee has ex officio members and representation from liaison organizations, such as the American Medical Association and the American Academy of Pediatrics.[14] Although the ACIP generally holds meetings 3 times per year, during which they develop the childhood and adult immunization schedules and make recommendations for vaccine use in the United States, they have been meeting monthly to prepare recommendations for COVID-19 vaccines.[14] The ACIP convened and recommended the Pfizer and Moderna vaccines before the issuance of an EUA by the FDA.

COVID-19 Vaccine Allocation

With vaccines available, several considerations need to be taken to ensure fair and equitable access to this limited resource. The ACIP has provided recommendations on

which groups should be prioritized for the earliest allocations of the vaccine. These recommendations were centered around 4 ethical principles: (1) maximize benefits and minimize harms, (2) promote justice, (3) mitigate health inequities, and (4) promote transparency.[15] A phased allocation of vaccines is planned. On December 2, 2020, the ACIP voted and stated that when a COVID-19 vaccine is authorized by the FDA and recommended by the ACIP, vaccination in the initial phase of the COVID-19 vaccination program (Phase 1a) should be offered to health care personnel and residents of long-term care facilities. This will be followed by those in phase 1b, which consists of frontline essential workers and persons age 75 years and older. Phase 1c will include persons age 65–74 years and those age 16–64 with high-risk conditions. Finally, phase 2 will include all other healthy adults.

Take Home Message

The COVID-19 vaccines that are first made available to health care personnel and residents of long-term care facilities, followed by other individuals at high risk for complications of COVID-19, have met rigorous efficacy and safety standards with no shortcuts taken in their development. It is essential to actively address the spread of distrust and misinformation surrounding vaccines for COVID-19. Clinicians must feel comfortable educating patients that all of the appropriate steps are being taken to ensure that the COVID-19 vaccine is safe and effective, to help dispel vaccine hesitancy among patients.

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