Anticipating Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Testing, Licensure, and Recommendations for Use

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The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China and its rapid spread throughout the world, inflicting enormous morbidity and mortality, clearly highlights the need for safe and effective vaccines.[1] Many countries and pharmaceutical companies are moving rapidly to design and test such vaccines; the World Health Organization has listed more than 120 candidates in various stages of development.[2] As we quickly embark on the pursuit of vaccines to prevent coronavirus disease 2019 (COVID-19), many are concerned that the rapidity with which these studies are being conducted will mean that vaccine safety will be sacrificed. However, over the past several decades, existing procedures to test and license vaccines, to regulate their production and purity, and advisory bodies to guide their use have been established and refined and are well prepared to ensure safe and effective vaccines. In this brief review, we will outline these processes from our perspectives. Both of us have been working in the vaccine field for 4 decades; we provide reassurance that the process is well established and designed to provide safe and effective vaccines.

Phases of Vaccine Development

Similar to the development of pharmaceutical agents, vaccine development progresses through preclinical and 3 distinct clinical stages, Phase 1, 2, and 3.[3,4]

Preclinical Studies

First comes the development of a vaccine candidate with the potential to stimulate a protective immune-CoV- response that will prevent disease upon encounter with the pathogen. SARS-CoV-2 is a new coronavirus, and we do not have a clear understanding of what is needed for a protective immune response. For many vaccines, the generation of an antibody directed to an important component of the virus is associated with protection. In the case of SARS-CoV-2, most candidate vaccines have been designed to generate an immune response to the spike protein, the attachment protein of the virus. Proposed vaccine constructs present the spike antigen as mRNA or DNA, as part of a nonreplicating or replicating viral vector such as adenovirus or vesicular stomatitis virus, as an inactivated whole virus, or as a purified protein.[5,6]

Initially, these proposed vaccines are administered in preclinical studies to small animals, often mice, and their immune responses are measured. Generation of immunity against the virus must be demonstrated or the vaccine would not undergo further testing. Toxicity studies also are conducted in animals to detect safety signals. With SARS-CoV-2, non-human primates increasingly are being used for studies in which vaccination is followed by challenge of the animals with wild-type SARS-CoV- 2.[7,8] Because of concerns raised about enhanced disease after wild virus infection in animal studies following vaccination against severe acute respiratory syndrome coronavirus 1 and Middle East respiratory syndrome-coronavirus,[9,10] experts have met and proposed immunologic criteria to be evaluated in animals and humans to detect and consequently reduce the risk of enhanced disease.[11] These criteria include the generation of functional antibody capable of virus neutralization and T-lymphocyte responses with a TH1 phenotype.

Phase 1 Clinical Trials

When preclinical studies in animals demonstrate that the vaccine stimulates an immune response and there are no toxicity concerns, vaccines then undergo Phase 1 clinical trials. Phase 1 study proposals must be presented to the US Food and Drug Administration (FDA) and approved before the start of the study. These trials enroll limited numbers of healthy subjects, usually fewer than 100 individuals, between the ages of 18 and approximately 55 years primarily to test the safety of the new experimental vaccine, although immunogenicity is also measured. Subjects enrolled in Phase 1 studies are well informed about the risks and the potential benefits of the vaccines and are screened for their ability to be monitored closely and to adhere to rigorous safety assessments. These assessments include daily monitoring of local and systemic adverse events with measurement of temperature, size of redness and swelling at the injection site, and with detailed

ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
DSMC	Data Safety and Monitoring Committee
FDA	US Food and Drug Administration
NVICP	National Vaccine Injury Compensation Program
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VRBPAC	Vaccine and Related Biologic Products Advisory Committee

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assessments of systemic reactions resulting in limitations of normal activities after vaccine administration. Phase 1 studies also often involve dose-ranging studies, so that the first enrolled subjects are administered the lowest doses of vaccine and if tolerated, the doses are increased.

All Phase 1 studies include a Data Safety and Monitoring Committee (DSMC) composed of vaccine experts, independent of the study-site investigators and sponsors of the study, who assess the reactions and approve the advancing of the dose level based on the safety profile of the administered vaccines. All Phase 1 studies also have halting rules, so that if severe reactions are seen, the study will be stopped. These halting rules might include hospitalization for a vaccine-related event or a severe reaction attributed to the vaccine in several participants. All participants in the trials have immunologic studies performed as well to determine the height of the antibody responses, the function of the antibody generated, and T-lymphocyte responses to the vaccines.

As mentioned previously, the sample sizes of these Phase 1 studies are usually fewer than 100 individuals, based on the safety of the administered vaccine and the doses that are proposed to be tested. Some of the Phase 1 studies evaluating SARS-CoV-2 vaccines also have included individuals older than 65 years of age to assess safety and immunogenicity in this population, which is at greater risk for severe COVID-19. At the conclusion of the Phase 1 trial, the safety and immunogenicity data are reviewed and presented to the FDA for approval to advance to Phase 2 studies.

Phase 2 Clinical Trials

Phase 2 studies involve several hundred subjects and often have a larger age range than Phase 1 trials. With SARS-CoV-2 vaccines, Phase 2 studies are planned to expand the safety profile and to assess immune responses in larger numbers of subjects. Again, meticulous attention to safety assessment is included in these studies, also with the input of independent DSMCs to assess the reaction profile. Finally, if Phase 2 studies confirm safety and immunogenicity in the expanded populations and with approval of the FDA, Phase 3 trials can begin.

Phase 3 Clinical Trials

Phase 3 trials are designed to determine whether the vaccines will prevent a predefined end point, generally the prevention of laboratory-confirmed disease. Subjects enrolled in Phase 3 studies are randomized and blinded to receipt of either vaccine or a control, usually consisting of a placebo. Subjects and investigators also are blinded to group assignment and remain so throughout the Phase 3 trial. After injection, study participants are followed closely, and if they should develop predefined symptoms of disease, they are tested for the presence of the virus.

The determination of the primary end point of the study and the accepted level of vaccine efficacy of the vaccine for the study can be a complicated endeavor. The World Health Organization and other international groups are advocating for standard definitions for the efficacy trials and standard immunologic assays assessing the SARS-CoV-2 vaccine responses so that the multiple tested vaccines ultimately can be compared with each other. The Phase 3 efficacy trials planned for SARS-CoV-2 vaccines in the US are expected to enroll 20 000 to 30 000 individuals, the numbers projected to be necessary to determine whether the vaccines will prevent significant disease over a period of 6 months' follow-up. Obviously, this will depend on the attack rate in the control group, with greater rates of infection associated with less time needed to determine vaccine efficacy. Each trial will be targeted for a defined number of cases detected and when that number of cases has been reported, the efficacy will be assessed. Ideally, one of the results of the phase 3 trial will be determination of a serologic correlate of protection. For example, a correlate could be an antibody level associated with protection from disease. This would facilitate evaluation of the vaccine in population groups not involved in the original trial, such as children, because it would not require assessment of actual protection from disease. Although this is a highly sought-after end point, it is not always possible to validate such a correlate of protection.[12]

Licensing a Vaccine

At the conclusion of the Phase 3 efficacy trial the study data will be presented to the FDA, who ultimately will decide whether the vaccine will be licensed. The level of efficacy that will be accepted for licensure of a SARS-CoV-2 vaccine remains a complicated question. In the face of the outbreak, would a vaccine that is 50% efficacious be acceptable for licensing? Those decisions will be part of the licensure process. The FDA also will require the vaccine producer to label the product for how it will be used, based on the data generated in the Phase 3 clinical trial. The FDA will seek the guidance of a standing advisory group of experienced clinicians, vaccine experts, epidemiologists, and other subject matter experts, called the Vaccine and Related Biologic Products Advisory Committee (VRBPAC), to advise the FDA whether the vaccine should be licensed. VRBPAC often has 1 or 2 pediatricians as members. The FDA poses specifically focused questions to the VRBPAC that relate to both vaccine efficacy and vaccine safety. All the adverse events reported in clinical trials will be comprehensively presented and discussed with the committee. Any significant safety concern raised may delay licensure or additional safety studies may be proposed. Ultimately, the FDA will seek the guidance of the VRBPAC but will decide as an agency whether the vaccine will be licensed and what limitations will be placed on the licensure.

The inclusion of children and pregnant women in vaccine licensure will not occur unless the vaccines have been studied in those populations for their safety and immunogenicity. Although children have had less severe disease than adults, the recent identification of the multisystem inflammatory syndrome in children after SARS-CoV-2 infection, the concerns for more severe disease in children with underlying

medical conditions, and the overall desire to prevent COVID-19 in children should stimulate vaccine studies in children. Such studies will be planned after the experimental vaccines have been shown to be safe and immunogenic in the targeted Phase 1 and 2 clinical studies in healthy adults. Older healthy children without underlying conditions will be studied first, with progression to younger children as both safety and immunogenicity are demonstrated. Pediatricians experienced in vaccine evaluation will be included in DSMCs and will be a part of this process to carefully monitor the safety of the vaccines as they are meticulously assessed in children. Although epidemiologic studies in pregnant women do not demonstrate increased severity of COVID-19 when compared with nonpregnant women, vaccines should also be evaluated in pregnant women. Obstetricians skilled in vaccine studies will be included in the DSMCs for studies in pregnant women. Because organogenesis occurs in the first trimester of pregnancy, vaccine studies should begin in healthy pregnant women in the second and third trimesters of pregnancy and the safety and immunogenicity evaluated.

Vaccine Manufacturing and Deployment

Given the constrained timeline for testing and the need for rapid deployment of the SARS-CoV-2 vaccines, manufacturing capabilities will need to be established before the conclusion of the efficacy trials. This will entail financial outlays for building production facilities for new vaccines before they have been shown to be effective. For example, because there are no existing licensed vaccines using the mRNA or DNA technology, these manufacturing facilities would need to be established should these constructs move toward licensure. Globally, most vaccines are manufactured by 5 companies based in the US and Europe,[13,14] geographically at a distance from underserved areas in which SARS-CoV-2 vaccines are needed. Financial support from governments, nongovernmental organizations, and philanthropic organizations will be needed during this time to produce the required number of vaccines to fully immunize the 7 billion inhabitants of the world. To facilitate rapid availability of COVID-19 vaccines, the US government has agreed to finance production of millions of doses of vaccine before completion of the phase 3 trials for promising candidates.[15] This reduces manufacturer risk, should the vaccine be found ultimately not to merit licensure.

In addition, most vaccines are administered by a healthcare worker via needle and syringe, and this approach undoubtedly will be used for many COVID-19 vaccines. It will be challenging to rapidly mobilize a large experienced vaccinator workforce during a pandemic. Novel administration technologies also might include microneedle array patches, reconstitution administration devices, and jet injectors. Not requiring a needle and syringe could make it easier for non-technical persons to be trained to administer vaccine and to facilitate uptake, but innovative approaches to delivery also will need to be evaluated for safety and immunogenicity before they can be widely employed.

Key Issues of Vaccination Policy Making

Vaccines do not save lives. Vaccinations save lives. A vaccine dose that remains in the vial is 0% effective. Once a SARS-CoV-2 vaccine is licensed for use in the US, recommendations will need to be made as to who should receive it and who should not, any groups who should be at higher priority for vaccination compared with other groups, the optimal immunization schedule including addressing the need for boosters, catch-up vaccination for those older than those who would be recommended for ongoing routine vaccination, and more. Systems need to be in place to provide access to vaccines and to remove barriers to access, such as cost. Ongoing monitoring of vaccine effectiveness and safety are critical to evaluate issues, such as waning immunity, groups at heightened risk for vaccine failure, and to determine adverse events following vaccination that are causally related, especially rare events that could not be detected in prelicensure trials. Estimations of the burden of causally vaccine-related adverse events can then be weighed against the benefits of the vaccine to determine whether any changes in recommendations are warranted. Disease surveillance is crucial to determine who continues to acquire disease, risk factors for disease, and the role of vaccine failure versus failure to vaccinate in disease prevention.

The Advisory Committee on Immunization Practices Process

Following licensure of vaccines by the FDA, the group that has played the major role in determining recommendations for vaccination in the US is the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC).[16] The ACIP covers recommendations for children, adolescents, and adults. The Committee on Infectious Diseases of the American Academy of Pediatrics also has played a major role in formulating vaccination recommendations for children and adolescents. Since 1995, the ACIP, American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians, American College of Obstetricians and Gynecologists, and others have worked together to develop vaccination schedules for children, adolescents and adults, which are updated annually.[17]

Members of the ACIP have expertise in a variety of disciplines related to the charge to the committee. This usually includes, but is not limited to, the following disciplines: clinical medicine including pediatrics, epidemiology, vaccinology, public health, implementation science, and economic evaluations. The ACIP Charter states, "Committee deliberations on use of vaccines to control disease in the U.S. shall include consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of evidence reviewed, analyses and implementation issues. The committee may revise or withdraw their recommendation(s) regarding a particular vaccine as new information on disease epidemiology, effectiveness or safety, economic

considerations or other data become available."[18] Once approved by the CDC Director, the recommendations are published in the *Morbidity and Mortality Weekly Report* (*MMWR*) and become official CDC immunization use policy. Among the responsibilities of the ACIP is prioritizing use in settings in which there are shortages of vaccines so that the highest-priority groups for whom vaccine might be recommended can receive them.

The vaccination system in the US consists of public and private providers. Most vaccines for children are delivered by private healthcare providers, although many of the vaccines are purchased using federal or other government funds. The Vaccines for Children Program is an entitlement program for all ACIP approved vaccines for eligible children.[19,20] Eligible children include those on Medicaid, those who are completely uninsured, and American Indian/Alaskan Natives. Approximately 50% of children are covered by Vaccines for Children.[21] In addition, Federal grants to states can be used to purchase vaccines to cover other children.[22] The Affordable Care Act requires private insurers to cover ACIP recommended vaccines at in-network providers.

Critical Questions That Need to Be Answered Following Vaccine Licensure and Use

Clinical trials usually are conducted with thousands of participants and in some trials, tens of thousands, as planned with SARS-CoV-2 vaccines. However, once approved for use, vaccines may be recommended for 100s of millions of persons. Several questions may not be answered in the clinical trials. These questions include: (1) What is the duration of protection from disease and the potential need for boosters. (2) What is the effectiveness of vaccine in population groups not evaluated in the clinical trials. For example, an efficacy trial may take place in adults but the vaccine was licensed for use in young children based on immunogenicity data. Clinical effectiveness can be measured in observational post-licensure studies by determining the incidence in vaccinees vs non-vaccinees. (3) Are there rare causally related adverse events and if so, what is the incidence rate and are there risk factors for developing the adverse event that could lead to vaccine contraindications. (4) What is the impact of vaccination in protecting the community (ie, herd immunity) by preventing transmission. Answering these questions requires a comprehensive surveillance system to detect and determine characteristics of disease in the post-vaccine era and whether such disease is the result of failure to vaccinate or vaccine failure. If the former, what measures can be taken to enhance vaccine uptake, or should recommendations for vaccination be broadened if substantial numbers of cases are occurring in groups for whom vaccine is not recommended? If there is evidence of vaccine failure, is it the result of vaccine mishandling (eg, improper storage) or is the rate of failure within expected levels (eg, the measured vaccine effectiveness is within levels expected based on the pre-licensure trials)? If effectiveness is low, are there groups at greater risk for vaccine failure, and if so, would additional doses of vaccines or alternative schedules reduce that risk?

Adequately assessing vaccine safety is critical to the success of immunization programs and requires an existing comprehensive system to monitor safety. In the US, there are several systems in place to assess safety in the post-licensure setting.[23] These include Vaccine Adverse Event Reporting System, a system that allows providers, parents, and patients to report adverse events. The Vaccine Adverse Event Reporting System functions more to raise hypotheses about whether receipt of a vaccine or vaccines causes the adverse event rather than to evaluate causation. The Vaccine Safety Datalink is a collaborative project between CDC's Immunization Safety Office and 8 healthcare organizations. The Vaccine Safety Datalink was initiated in 1990 and continues today to monitor safety of vaccines over large populations and to conduct studies to assess rare and serious adverse events following immunization. The Center for Immunization Safety Assessment is a national network of vaccine safety experts from the CDC's Immunization Safety Office, 7 medical research centers, and other partners, which provides a comprehensive vaccine safety public health service to the nation.

Most vaccine-preventable diseases are transmitted person-to-person. Thus, when some individuals are vaccinated with most vaccines they are not only themselves getting an active immune response from the vaccine but also indirectly are protecting others in society who either cannot be vaccinated (eg, have medical contraindications to vaccine) or fail to make an adequate immune response.[24] Therefore, if someone is injured by vaccine, society owes that person compensation. This is the basis for the National Vaccine Injury Compensation Program (NVICP).[25] This program offers compensation for the injured vaccine recipient and reduces the risk of liability for the vaccine provider and the manufacturer because persons who receive vaccines covered by the NVICP must first go through this compensation process, and suing the provider or manufacturer is difficult. The NVICP has markedly reduced liability. During the last pandemic in 2009 of H1N1 influenza, post-licensure vaccine safety systems were established to efficiently monitor vaccine safety. It is anticipated that similar systems also will be implemented as the new SARS-CoV-2 vaccines are introduced.[26,27]

Few programs have had impact close to that of vaccines in reducing health burdens. This is the result of a rigorous system to assure that vaccines recommended are safe and effective, and of an equally rigorous system to assure that persons for whom vaccines are recommended actually receive them. ■

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al, China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Draft landscape of COVID-19 candidate vaccines, June 2, 2020. Cited June 8, 2020. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed June 8, 2020.
3. Edwards KM, Hackell JM, Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine. Countering vaccine hesitancy. Pediatrics 2016;138:e20162146.
4. The College of Physicians of Philadelphia. The history of vaccines. https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation. Accessed June 8, 2020.
5. Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. Immunity 2020;52:583-9.
6. Diamond MS, Pierson TC. The challenges of vaccine development against a new virus during a pandemic. Cell Host Microbe 2020;27:699-703.
7. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Rapid development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;eabc1932.
8. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science 2020;eabc6284.
9. Graepel KW, Kochhar S, Clayton EW, Edwards KM. Balancing expediency and scientific rigor in SARS-CoV-2 vaccine development. J Infect Dis 2020;jiaa234.
10. Graham BS. Rapid COVID-19 vaccine development. Science 2020;368:945-6.
11. Consensus considerations on the assessment of the risk of disease enhancement with COVID-19 vaccines [Internet]. 2020 Apr. https://brightoncollaboration.us/brighton-collaboration-cepi-covid-19-web-conference/. Accessed June 8, 2020.
12. Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol 2010;17:1055-65.
13. Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing—An overview. Vaccine 2017;35:4064-71.
14. Gomez PL, Robinson JM. Vaccine manufacturing. In: Plotkin S, Orenstein W, Offit P, Edwards K, eds. Plotkin's vaccines. 7th ed. Philadelphia (PA): Elsevier; 2018. p. 51-60.
15. Weiland N, Sanger DE. White House Narrows Candidates for Vaccine to Five Companies. New York (NY): New York Times; 2020.
16. Walton LR, Orenstein WA, Pickering LK. The history of the United States Advisory Committee on Immunization Practices (ACIP). Vaccine 2015;33:405-14.
17. Centers for Disease Control and Prevention. ACIP recommendations. https://www.cdc.gov/vaccines/acip/recommendations.html. Accessed June 8, 2020.
18. Centers for Disease Control and Prevention. ACIP charter. https://www.cdc.gov/vaccines/acip/committee/charter.html. Accessed June 8, 2020.
19. Cohn A, Rodewald LE, Orenstein WA, Schuchat A. Immunization in the United States. In: Plotkin S, Orenstein W, Offit P, Edwards K, eds. Plotkin's vaccines. 7th ed. Philadelphia (PA): Elsevier; 2018. p. 1421-40.
20. Centers for Disease Control and Prevention. Vaccines for Children Program (VFC). https://www.cdc.gov/vaccines/programs/vfc/. Accessed June 8, 2020.
21. Whitney CG, Zhou F, Singleton J, Schuchat A. Benefits from immunization during the Vaccines for Children program era—United States, 1994-2013. MMWR Morb Mortal Wkly Rep 2014;63:352-5.
22. Protecting the Public's Health. Critical Functions of the Section 317 Immunization Program—A Report of the National Vaccine Advisory Committee. Public Health Rep 2013;128:78-95.
23. Centers for Disease Control and Prevention. Vaccine Safety Datalink (VSD). www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html. Accessed June 8, 2020.
24. Fine PEM, Mulholland K, Scott JA, Edmunds WJ. Community protection. In: Plotkin S, Orenstein W, Offit P, Edwards K, eds. Plotkin's vaccines. 7th ed. Philadelphia (PA): Elsevier; 2018. p. 1512-31.
25. Levine EM, Davey AS, Houstan AM. Legal issues. In: Plotkin S, Orenstein W, Offit P, Edwards K, eds. Plotkin's vaccines. 7th ed. Philadelphia (PA): Elsevier; 2018. p. 1601-30.
26. McCarthy NL, Gee J, Weintraub E, Donahue JG, Nordin JD, Daley MF, et al. Monitoring vaccine safety using the Vaccine Safety Datalink: utilizing immunization registries for pandemic influenza. Vaccine 2011;29:4891-6.
27. Yih WK, Lee GM, Lieu TA, Ball R, Kulldorff M, Rett M, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. Am J Epidemiol 2012;175:1120-8.