tomy group, but it is possible that this difference was driven, at least in part, by postoperative instructions.

In practical terms, because patients may appropriately prioritize different outcomes, the pros and cons of all treatment options should be presented and discussed. Considering that laparoscopic appendectomy is a highly effective therapy — rapidly resolving pain and allowing patients to return to normal activities while avoiding the subsequent risks of recurrent appendicitis and hospitalization — I believe that most providers would recommend surgical treatment for uncomplicated appendicitis if that option is available. I know I would.

However, as the authors suggest, circumstances do matter, and advantages of antibiotic treatment relative to surgery may be greater during the Covid-19 pandemic or other public health emergencies in which operating room capacity and other resources are severely constrained. The American College of Surgeons has recently released guidance on triage for nonemergency surgical procedures during the Covid-19 pandemic, suggesting that hospitals and surgical centers should consider, among other factors, the needs and informed preferences of patients, medical risks that might be incurred by delaying operation, resource availability, capacity, and safety.[5]

In addition to affecting the provision of surgical and medical care, the pandemic has highlighted ongoing, dreadful health care disparities in the United States and the adverse impact of social determinants, as well as structural bias and racism, on health and health outcomes. It will be important to ensure that some people, in particular vulnerable populations, are not offered antibiotic therapy preferentially or without adequate education regarding the longer-term implications. Flum and colleagues highlight the importance of "individual characteristics, preferences, and circumstances" in making decisions based on their findings. Included among these considerations should be the effects of race or ethnic group, location, insurance status, and socioeconomic status,[6-9] which may affect quality of life[10,11] and lead to poorer outcomes for some people.

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The Covid-19 Vaccine-Development Multiverse

Penny M. Heaton, M.D.

Leaving in its wake more than 12 million infections, over 550,000 deaths, and an economic toll in the trillions of dollars to date,[1] the SARS-CoV-2 pandemic has devastated the most vulnerable in our society — adults 65 years of age or older, persons with underlying conditions, and the ec-

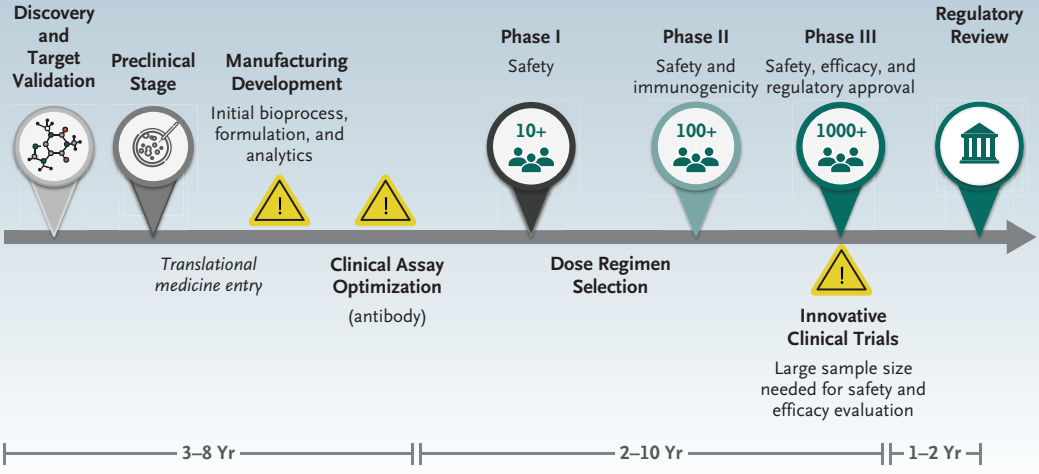

Figure 1. Traditional Vaccine Development Pathway.

onomically deprived.[2] A vaccine is urgently needed to prevent Covid-19 and thereby stem complications and deaths resulting from transmission of the disease.

Jackson et al. now report in the *Journal* preliminary findings from a phase 1 trial to evaluate the safety and immunogenicity of an mRNA SARS-CoV-2 vaccine.[3] Phase 1 involves 45 healthy adults, 18 to 55 years of age, who were assigned to receive the candidate vaccine at one of three dose levels (25 μg, 100 μg, or 250 μg) given as two vaccinations 28 days apart. These preliminary findings represent the first of three reports of data from a phase 1 study of this candidate vaccine; a second report including similar data from adults older than 55 years of age and a final report summarizing the safety and durability of immunity for both study cohorts are also planned.

The speed with which this vaccine has been developed is remarkable — from publication of the first SARS-CoV-2 sequences through phase 1 in 6 months, as compared with a typical timeline of 3 to 9 years (Fig. 1). The rapid pace of development of vaccines against Covid-19 is enabled by several factors: prior knowledge of the role of the spike protein in coronavirus pathogenesis and evidence that neutralizing antibody against the spike protein is important for immunity[4,5]; the evolution of nucleic acid vaccine technology platforms that allow creation of vaccines and prompt manufacture of thousands of doses once a genetic sequence is known[6]; and development activities that can be conducted in parallel, rather than sequentially, without increasing risks for study participants.

The safety and immunogenicity data in this preliminary report are promising, and they support continued development of this vaccine. However, we must bear in mind the complexity of vaccine development and the work still to be done before Covid-19 vaccines are widely available.

Many phase 3 studies fail because of incorrect identification of the dose that best balances safety and efficacy.[7] The dosing regimen for this mRNA vaccine is still under study. The 250-μg dose did not appear to be associated with markedly higher antibody titers than the 100-μg dose, but it was associated with a higher proportion of severe systemic adverse events. As the investigators indicate, it is prudent to evaluate doses of 100 μg and lower to define the regimen that provides the most appropriate benefit–risk profile for this vaccine. Another special dosing consideration in this case is age: the immune functions that decline with age and that are likely to be responsible for the greater risk of severe Covid-19 in older adults may also lead to poor vaccine responses. Will a high-dose Covid-19 vaccine be needed for effective protection of older adults, as observed with influenza vaccines?[8]

The clinical significance of SARS-CoV-2 bind-

ing and neutralizing antibody titers and their ability to predict efficacy will need to be confirmed. These measures are currently being used to guide dose selection before being verified; they are the best tools available and are supported by findings in nonhuman primates.[9] Confirmation of the correlation between antibody titers and protection against Covid-19 will be possible only in a large clinical efficacy study. In the meantime, the validity of the assays for measuring antibody will also need to be documented. These assays are notoriously variable because they use live virus or protein expression in cell culture with a readout that relies on an in vitro biologic reaction (i.e., serum antibodies binding or killing viral antigen). Optimization of the performance characteristics of these assays will be invaluable in streamlining further development and supporting bridging across varied populations and manufacturing processes.

The authors indicate that a planned phase 3 trial of this mRNA SARS-CoV-2 vaccine is imminent; the trial will require thousands of subjects in order to confirm the safety of the vaccine and to show statistically robust efficacy in preventing Covid-19. The operational complexity inherent in a large study is compounded by the undulations of the pandemic; efficacy can be determined only if there is a match between the location of vaccinated participants and pandemic hot spots. Uncertainty regarding the expected efficacy profile also drives complexity; the profiles observed for other viral vaccines suggest that efficacy against severe Covid-19 may be higher than efficacy against mild disease. Careful selection of primary end points and event-driven study designs with the possibility of sample size reestimation should be considered.

Accelerating the development of Covid-19 vaccine candidates beyond phase 1 depends on continued parallel tracking of activities and fulsome resources. The world has now witnessed the compression of 6 years of work into 6 months. Can the vaccine multiverse do it again, leading to a reality of a safe, efficacious Covid-19 vaccine for the most vulnerable in the next 6?

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