

## EDITORIAL



## SARS-CoV-2 Vaccination — An Ounce (Actually, Much Less) of Prevention

Eric J. Rubin, M.D., Ph.D., and Dan L. Longo, M.D.

The Covid-19 epidemic continues to rage, especially in countries that have been unable or unwilling to institute strong public health measures. A return to normality has increasingly come to rely on the success of vaccines to prevent disease and, we hope, limit further spread of infection. However, this hope has been tempered by several unknowns. No existing vaccines have been shown to be effective against infection with any betacoronavirus, the family that includes SARS-CoV-2, which causes Covid-19. SARS, caused by another betacoronavirus, ended on its own before serious efforts at vaccine development were undertaken, and the rather small number of MERS cases has not yet justified the large-scale effort and investment required to determine whether preclinical vaccine candidates are efficacious. In addition, strategies to increase the speed of vaccine development have themselves had only limited testing. A relatively small number of people have received adenovirus-vectored vaccines, and no vaccines based on mRNA technologies have yet been approved. Would these new products be effective and safe?

Today we have part of the answer, and it is strongly encouraging. The vaccine BNT162b2 is a modified RNA that encodes a version of the SARS-CoV-2 spike protein containing mutations that lock the protein into a conformation that can induce neutralizing antibody responses. Early clinical trials showed that it could induce both humoral and cellular immunity, although we did not know until now whether these responses would protect against symptomatic infection. Today we know.

We are publishing today in the *Journal* the re-

sults of a phase 3, double-blind, randomized, controlled trial of a new RNA vaccine.<sup>1</sup> In this trial, 21,720 participants received BNT162b2 and 21,728 received placebo. Both groups received two injections spaced 21 days apart. Persons with obesity or other coexisting conditions were well represented, and more than 40% of participants were older than 55 years of age. Participants notified trial sites if they had symptoms that were consistent with Covid-19, and they were tested to diagnose infection. They recorded in daily diaries any adverse events they were experiencing. The primary outcomes were safety and the incidence of symptomatic Covid-19 with onset occurring at least a week after the second dose of vaccine or placebo, although all symptomatic infections are reported. The findings in this report include the first 170 cases of Covid-19 detected in the primary population and cover a median of 2 months of safety data. The investigators plan to continue to follow the participants, although once the vaccine becomes freely available, maintaining randomization may be a challenge.

The results were impressive. In the primary analysis, only 8 cases of Covid-19 were seen in the vaccine group, as compared with 162 in the placebo group, for an overall efficacy of 95% (with a 95% credible interval of 90.3 to 97.6%). Although the trial does not have the statistical power to assess subgroups, efficacy appeared to be similar in low-risk and high-risk persons, including some from communities that have been disproportionately affected by disease, and in participants older than 55 years of age and those younger than 55. Adverse events were largely consistent with vaccine reactogenicity, with mostly transient and mild local

reactions such as injection-site pain and erythema; systemic reactions such as fever, fatigue, and adenopathy were uncommon. This pattern appears to be similar to that of other viral vaccines and, at least with this number of participants and this follow-up period, does not arouse specific concern.

There are nonetheless minor issues. The number of severe cases of Covid-19 (one in the vaccine group and nine in the placebo group) is too small to draw any conclusions about whether the rare cases that occur in vaccinated persons are actually more severe. For practical reasons, the investigators relied on trial participants to report symptoms and present for testing. Since reactogenicity was more common in vaccine recipients, it is possible that they were less inclined to believe that minor symptoms were due to Covid-19 and therefore less likely to refer themselves for testing. And some important data, such as the rate of asymptomatic disease (as measured by seroconversion to a viral nucleoprotein that is not a component of the vaccine), have not yet been reported.

Nevertheless, the trial results are impressive enough to hold up in any conceivable analysis. This is a triumph. Most vaccines have taken decades to develop, but this one is likely to move from conception to large-scale implementation within a year. The sequence of the virus that led to the development of the specific antiviral RNA sequence required to design the vaccine didn't become known until it had been determined and widely disseminated by the Chinese Center for Disease Control and Prevention in January 2020. There is a lot of credit to go around: to the scientists who shared data and who developed the underlying methods and implemented them to create a vaccine, to the clinical trialists who performed high-quality work in the setting of a health emergency, to the thousands of participants who volunteered to take part in the trial, and to the

governments that helped create performance standards and a market for the vaccine. And all this stands as a template for the many other Covid-19 vaccines currently in development, some of which have already completed their phase 3 trials.

Important questions of course remain. Only about 20,000 people have received this vaccine. Will unexpected safety issues arise when the number grows to millions and possibly billions of people? Will side effects emerge with longer follow-up? Implementing a vaccine that requires two doses is challenging. What happens to the inevitable large number of recipients who miss their second dose? How long will the vaccine remain effective? Does the vaccine prevent asymptomatic disease and limit transmission? And what about the groups of people who were not represented in this trial, such as children, pregnant women, and immunocompromised patients of various sorts?

The logistic challenges of manufacturing and delivering a vaccine remain daunting. This vaccine, in particular, requires storage at  $-70^{\circ}\text{C}$ , a factor that may limit its deployment in some areas. Nevertheless, the remarkable level of safety and efficacy the vaccine has demonstrated thus far make this a problem that we should welcome solving. What appears to be a dramatic success for vaccination holds the promise of saving uncounted lives and giving us a pathway out of what has been a global disaster.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

This editorial was published on December 10, 2020, at NEJM.org.

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 Covid-19 vaccine. *N Engl J Med*. DOI: 10.1056/NEJMoa2034577.

DOI: 10.1056/NEJMe2034717

Copyright © 2020 Massachusetts Medical Society.