EDITORIAL

A New Vaccine to Battle Covid-19

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The United States and many parts of the world have now lost control of the Covid-19 pandemic owing to the respiratory spread of SARS-CoV-2 and to inconsistent adherence to effective public health measures, including wearing masks and maintaining social distancing. Persons infected with SARS-CoV-2 are frequently asymptomatic, yet they have high respiratory viral loads, and they are major purveyors of viral spread. These factors have led to the current explosion of Covid-19 hospitalizations and deaths, with Covid-19 now a major cause of death in the United States. Our only hope is safe and effective vaccines that can be widely deployed to provide herd immunity that can control viral spread.

Since January 2020, when the first sequencing of SARS-CoV-2 became public, the scientific community has worked toward rapid development of mRNA, protein, viral vector, and other types of Covid-19 vaccines. Two vaccine efficacy trials have been completed, and the two vaccines have recently received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA). The first vaccine given such authorization, an mRNA in lipid nanoparticles (LNPs), BNT162b2 from Pfizer and BioNTech, showed 95% vaccine efficacy.[1] Today, the *Journal* is publishing the trial results establishing the efficacy of a second mRNA-LNP vaccine, mRNA-1273 from Moderna.[2] In the mRNA-1273 Coronavirus Efficacy (COVE) trial, 30,420 volunteers were randomly assigned to receive either vaccine or placebo (15,210 in each group). Symptomatic Covid-19 was confirmed in 185 participants in the placebo group and 11 in the mRNA-1273 group, for a vaccine efficacy of 94.1% (95% confidence interval, 89.3 to 96.8). For participants 18 to less than 65 years of age, the efficacy was 95.6%, and for those 65 years or older the efficacy was 86.4%. Both the Moderna vaccine and the Pfizer–BioNTech vaccine begin to protect recipients approximately 10 days after the first dose, with maximum protection after the second dose.

The safety profile of the mRNA-1273 vaccine for the median 2-month follow-up showed no safety concerns; the frequency of unsolicited adverse events and severe adverse events during 28 days after injection was similar in the vaccine and placebo groups. Solicited adverse events at the injection site occurred more frequently with the vaccine than with placebo, occurring in 88.6% of vaccinees after the second dose. The safety and immunogenicity of the mRNA-1273 vaccine in older adults has been previously reported.[3]

One of the concerns regarding Covid-19 vaccines that has emerged from studies of the earlier SARS and Middle East respiratory syndrome (MERS) outbreaks is the possibility that a Covid-19 vaccine could enhance disease, a phenomenon called vaccine-associated enhanced disease (VAED).[4,5] In the COVE trial, severe Covid-19 developed in 30 participants, all in the placebo group; thus, the mRNA-1273 vaccine provided 100% protection against severe Covid-19 disease, with no evidence of VAED.[2] In the earlier SARS and MERS preclinical studies, VAED occurred with low neutralizing antibodies.[4,5] Thus, it will be important for the FDA and the Centers for Disease Control and Prevention to continue to monitor clinical trials for safety after issuing an EUA, including assessment of VAED risk.

Several major issues remain regarding the

ability of Covid-19 vaccines to mitigate the SARS-CoV-2 pandemic. First, what are the nature and the duration of the protective immune response to SARS-CoV-2? Evidence in vaccinated monkeys suggests that SARS-CoV-2 neutralizing antibodies are the primary mode of protection, and CD8 T-cell responses can augment protection.[6] How long neutralizing antibodies will last is not known, although follow-up studies in the phase 1 mRNA-1273 trial demonstrated persistence of neutralizing antibodies 3 months after the second dose of vaccine.[7] Second, 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 in the trial.[8] Third, analysis of virus escape from protective immune responses and long-term follow-up for rare safety events are needed.[4,5] Finally, the trial was not powered to determine whether mRNA-1273 could protect against asymptomatic SARS-CoV-2 infection, a question that is critical to controlling the pandemic. Studies designed to answer this question are ongoing or planned.

That the mRNA-1273 Covid-19 and the BNT162b2 Covid-19 vaccines protect with near-identical 94 to 95% vaccine efficacies — and that both vaccines were developed and tested in less than a year — are extraordinary scientific and medical triumphs. This happened because the scientific community was prepared from years of technology development for other vaccines, such as those against HIV, influenza, respiratory syncytial virus, and Zika, and because clinical trials consortia were established that rapidly carried out Covid-19 efficacy trials.[4,9] If mRNA-LNP vaccines significantly contribute to control of the pandemic, mRNA technology has the potential to radically change vaccine design for future viral outbreaks.

Although the Covid-19 pandemic is currently raging, the prospects for control of this and future pandemics are bright. The recent FDA issuance of EUAs for these extraordinarily protective vaccines provide us with much-needed hope at a time when so many are suffering. The next challenge is to get these and the next Covid-19 vaccines to the people most at risk as quickly as possible.

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

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