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News & Highlights

Coronavirus Variants—Will New mRNA Vaccines Meet the Challenge?

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On 24 February 2021, a month after announcing the project, the biotechnology company Moderna (Cambridge, MA, USA) sent samples to the US National Institutes of Health (NIH) of the updated coronavirus disease 2019 (COVID-19) vaccine booster it had created and manufactured to address the B.1.351 variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in South Africa [1]. The hope is that such quick updates to authorized vaccines will provide—if and as needed—protection against the rapidly spreading new strains of SARS-CoV-2 that have shown troubling signs suggesting immune evasion [2].

These vaccines and boosters highlight the unique advantages of the new, messenger ribonucleic acid (mRNA)-based vaccine development platform. Both Moderna and the partnership of Pfizer (New York City, NY, USA) and BioNTech (Mainz, Germany) tapped this novel technology to create and deliver COVID-19 vaccines in an unprecedented matter of months—in contrast to the typical timetable of years [3]. Now, the technology's speed and flexibility may prove doubly valuable by helping to meet the challenge of a swiftly evolving virus.

Several variants now spreading worldwide appear to transmit more easily between humans and are potentially more deadly [4]. In addition, some mutations may enable the virus to reinfect those who have recovered, with antibodies from people who have recovered from natural infections shown to be less protective against several of the new variants [5].

"The biggest concern I have is that the virus will continue to mutate in ways that evade immunity," said Hana Akselrod, an assistant professor of medicine and infectious disease specialist at the George Washington University School of Medicine in Washington, DC, USA. Some new variants "are a nightmare in that they seem—at least in test tube studies—to evade antibodies produced by prior infection or vaccination."

Coronaviruses, like all viruses, consist of a genome encased in a shell of proteins and fats [6]. The spike proteins on the outer surface of SARS-CoV-2 bind to human cells, where, after inserting its RNA genome, the virus hijacks the cellular machinery to make copies of itself. When released from hijacked cells (Fig. 1), newly copied viruses infect other cells and are shed to infect other hosts.

In the best case, the body successfully mounts an immune response by creating antibodies and specialized immune cells that stop the virus from infecting more cells, halting the disease. In surviving hosts, the immune system also remembers the virus and protects against reinfection. Because vaccines elicit—without causing disease—at least some of this immune response [7], they are critical tools in public health efforts against pandemics. As of February 2021, the World Health Organization listed 15 COVID-19 vaccines (including the two mRNA vaccines authorized for emergency use in the United States) in various stages of its approval process [8].

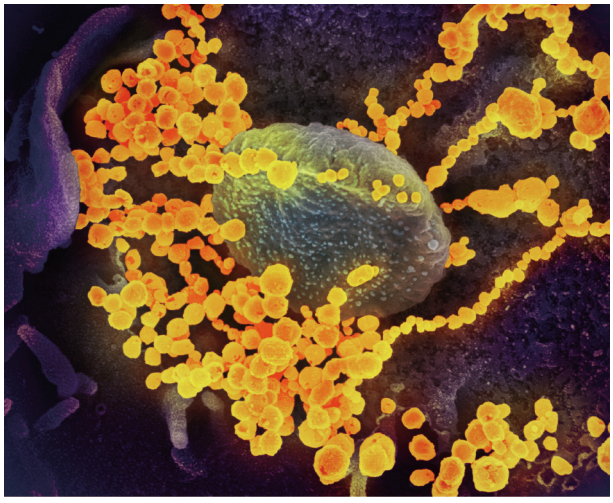

Fig. 1. In this scanning electron microscope image, the virus that causes COVID-19—SARS-CoV-2—is shown as round gold objects. The viruses are emerging from the surface of a host cell during the viral replication process. Credit: US National Institute of Allergy and Infectious Disease (CC BY 2.0).

Vaccines have a significant drawback, however. Their viral targets are actually moving ones and missing the mark can produce an inadequate immune response. Viruses are bad at copying their genomes, making lots of mistakes. The more infections, viruses, and copying, the greater the likelihood variants will evolve that can escape pre-existing immunity, either from infection or a vaccination. That means many of these evolving viruses—called variants, mutants, strains—may have changes that can make them easier to transmit, harder to neutralize, and more dangerous [9].

"Generally, most mutations that arise in a viral genome are either neutral or have negative value to the virus," said Akselrod. "But every once in a while, it will happen upon something that actually benefits it."

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Unlike traditional whole virus vaccines, mRNA vaccines can be quickly and relatively easily adjusted to target new variants. The mRNA platform takes advantage of mRNA translation, part of the natural process that cells use to turn genes into proteins. Vaccination delivers mRNA copies of the virus's spike protein (Fig. 2) wrapped in a lipid membrane [10]. Absorbing these lipid capsules, cells in the vaccinated person use the contained mRNA, which degrades after a few days, to create copies of the virus's spike protein [11,12]. Reacting against these spike proteins, the immune system makes antibodies against them, which mark the spike protein as "foreign," and also enlists immune cells in the fight. When the body sees these spike proteins, as happens when exposed to the actual virus, the immune system attacks the virus, preventing or reducing the risk of disease. Beyond COVID-19 vaccines, the technology also holds promise for vaccines against other infectious diseases like influenza and, possibly, acquired immune deficiency [13,14], as well as for anticancer therapies and fixes for gene-based diseases like sickle-cell anemia [14,15].

Large clinical trials have shown unprecedented effectiveness for the two US-authorized mRNA COVID-19 vaccines, both about 95% after the second dose [16]. This is much higher, for example, than the roughly 30%–50% effectiveness of the standard influenza vaccines offered each year [17]. Experts attribute this increased effectiveness, at least in part, to the ability of such gene-based vaccines to strongly engage the immune system's T-cells, which may more successfully create strong and long-lasting immunity [18,19].

Another gene-based vaccine platform, the one used to create the recently US-authorized (28 February 2021) Johnson and Johnson vaccine [20], uses a benign virus, an adenovirus, as a vector to deliver the spike protein code, which is then produced by infected cells. However, some people may have pre-existing immunity to adenoviruses, which can decrease the effectiveness of this approach. In addition, exposed to the same adenovirus vaccine again, a person's immune system may clear the adenovirus before it produces the spike protein, which could be a problem for booster shots developed with this platform to target new virus variants [21].

"Given a second time, antibodies directed against the viral vector might limit its ability to enter cells and deliver the gene that codes for the spike protein," said vaccine expert Paul A. Offit, attending physician and director of the Vaccine Education Center at Children's Hospital of Philadelphia in Pennsylvania, USA. "That is always a struggle."

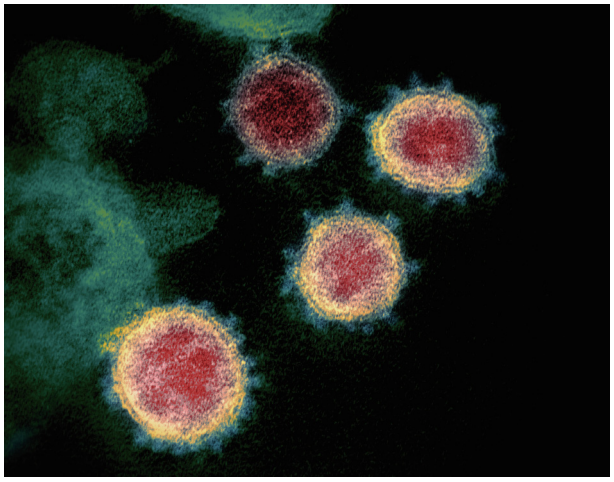

Fig. 2. A transmission electron microscope image of SARS-CoV-2 viruses, which cause COVID-19. The protrusions visible on the outside are the spike proteins that the virus uses to latch onto and enter its host's cells, and which are created in host cells—without the disease—by the mRNA vaccines to build immunity against the virus. Credit: US National Institute of Allergy and Infectious Disease (CC BY 2.0).

Laboratory-based experiments testing the Moderna and Pfizer–BioNTech vaccines suggest that they may be less effective against some variants but may still provide adequate protection, with antibodies elicited by both vaccines working well against the B.1.1.7 strain (first reported in the United Kingdom) but less well against the B.1.351 variant [5,22,23]. "The mRNA vaccines are starting at such a high level of protection that even if they are slightly less protective against the variants, it is still a high level of protection," said Anna Heffron, an MD–PhD candidate at the University of Wisconsin–Madison and member of a research team studying the immune response to SARS-CoV-2. In addition, these experiments do not account for cell-based immunity, which could provide critical protection against variants beyond that yielded by neutralizing antibodies alone [24]. Determining just how much of a threat the new variants actually pose might require clinical studies, such as one on-going in Austria [25] and possibly future variations of the controlled exposure trials now underway in the United Kingdom [26].

The key question for public health experts is whether people previously recovered or vaccinated will succumb to disease caused by the evolving variants. Called breakthrough infections, such events indicate a variant has escaped established immunity. If this occurs, Offit said, updated vaccines will likely be needed.

Identifying and tracking such emerging variants requires routine genetic analysis of virus samples, an effort in which the United States, like with COVID-19 testing generally [27], has lagged behind other countries. This increased need for viral genome sequencing has begun to be addressed, however, supported by new initiatives from the Biden administration [28].

In the simplest iteration, an mRNA booster vaccine would deliver an mRNA coding for the mutated spike protein [1]. "The mRNA vaccines are such amazing technology because they are so simple—it is just the code for the spike protein," said Akselrod. "In theory, changing that code to reflect the circulating spike protein should produce immunity to the variant."

In addition to such a single variant booster, Moderna has also created a multivalent mRNA vaccine combining the codes for the B.1.351 variant's and the original vaccine's spike proteins [1]. The company plans clinical trials to test this double-duty shot as both a booster for those already vaccinated and also as an initial vaccine. "By including multiple strains of SARS-CoV-2 in a vaccine, the virus theoretically might not be able to escape through mutation," Heffron said. "But we have not been able to test this yet."

Moderna, Johnson and Johnson, and Pfizer–BioNTech are all planning to test a third shot of their original vaccines as boosters to increase immunity against the variants [29]; Pfizer and BioNTech are also developing a clinical trial plan for an updated vaccine specifically targeting the B.1.351 strain and/or other variants [30].

Results from the phase 1 trial being performed by the US National Institutes of Allergy and Infectious Diseases with the booster formulation provided by Moderna in February 2021 are expected to be available in just a few months [1]. The trial will study the immune system's reaction to the shot but not wait for long-term results that would directly show protection from the virus [31]. The US Food and Drug Administration and the global Access Consortium of regulatory authorities have provided guidance that forgoes large, lengthy clinical trials and relies on immunological studies to prove effectiveness of the booster formulations, similar to the regulatory principles established for seasonal influenza vaccines [32,33]. Everyone is moving quickly in the face of the many questions about the virus and pandemic that remain unanswered, to try to anticipate what will be needed. "We are all just waiting for the virus to make its next move," Akselrod said.

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