



# Debunking mRNA Vaccine Misconceptions—An Overview for Medical Professionals

The hearts and minds of people worldwide have been consumed by the life-altering consequences of the Coronavirus disease 2019 (COVID-19) pandemic. Vaccine development is a cornerstone of the world's return to normalcy, and 2 mRNA-based vaccines have recently received Emergency Use Authorization from the Food and Drug Administration (FDA). Medical professionals have been offered these vaccines first due to their increased risk of infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19. Although work done at our University was instrumental in the development of mRNA vaccines,<sup>1</sup> we have encountered, among some medical staff, a reluctance to receive the vaccine.

While logistical hurdles such as scheduling and availability may decrease vaccine utilization, a sizeable number of health care staff have expressed reservations about vaccination. One concern is that mRNA vaccine technology is new and long-term adverse effects in humans are unknown. Vaccines are traditionally composed of inactivated virus, live-attenuated virus, or antigenic proteins. Normally, mRNA is transcribed from DNA and is then translated to protein. mRNA has not been historically widely used as a vaccine due to the lability of RNA, which is typically rapidly degraded by ribonucleases. The Moderna and Pfizer/BioNTech COVID-19 vaccines that received Emergency Use Authorizations mitigate this and other problems via the use of modified mRNA and lipid nanoparticles (LNPs).

The use of modified mRNA may be a source of concern for some. Nucleosides are the building blocks of DNA and RNA. Previous work has demonstrated that substitution of the nucleoside uridine for pseudouridine or N<sup>1</sup>-methylpseudouridine enhances the stability of mRNA and decreases immunogenicity, so these nucleosides are used in both COVID-19 mRNA vaccines.<sup>2-4</sup> Both of these modifications

are naturally occurring in eukaryotic cells, thereby mitigating concerns of toxicity.

To mediate its therapeutic effect, the mRNA in the vaccine must traverse the cell membrane and be translated to protein; however, cellular uptake of mRNA is limited because it is anionic. LNPs encapsulate RNA and facilitate cellular entry. The use of LNPs and liposomes is not limited to mRNA vaccines. These compounds have already been used in FDA-approved chemotherapies, vaccines, antifungals, and analgesics.<sup>5</sup>

Although there are no previously approved mRNA vaccines, these vaccines have been trialed in humans for oncologic therapies for nearly a decade (NCT01684241), and have been trialed in humans for infectious disease for over 3 years.<sup>6</sup> Regarding adverse events, data from phase I influenza mRNA vaccine and phase III COVID-19 mRNA vaccine trials have demonstrated that injection site pain, erythema, swelling, fever, fatigue, headache, chills, muscle pain, and arthralgia are more common in the vaccine group relative to placebo.<sup>3,4,6</sup> These events are consistent with reactogenicity, which is expected after immune system instigation.

The COVID-19 phase III mRNA-LNP vaccine trials have monitored most subjects for more than 2 months, suggesting that long-term adverse effects are unlikely. Moderna has enrolled >1700 volunteers in 12 previous Phase I/II trials, and they have not reported any long-term adverse events.<sup>7</sup> In the Moderna COVID-19 phase III vaccine trial data, the FDA did note an imbalance of cases of Bell's palsy in the vaccine group (n = 3) compared with the placebo group (n = 1). Only one case was ongoing; the rest were resolved or resolving.<sup>8</sup> In the Pfizer/BioNTech trial, 4 cases of Bell's palsy were noted in the vaccine group and none in the placebo group. One case resolved and the others were continuing/resolving.<sup>9</sup> This rate of Bell's palsy (0.02% for both trials) does not exceed the expected background rate of this disease. Furthermore, long-term adverse effects are unlikely mechanistically, because mRNA does not persist for an extended period of time or integrate into chromosomes.

Effective vaccines require an adequate immune response, so some vaccines include adjuvants to spur the

**Funding:** None.

**Conflicts of Interest:** None.

**Authorship:** Both authors have participated in the preparation of the manuscript.

Requests for reprints should be addressed to Frederick Hitti, MD, PhD, University of Pennsylvania, 3<sup>rd</sup> floor Silverstein, 3400 Spruce Street, Philadelphia, PA 19104.

E-mail address: [Frederick.Hitti@pennmedicine.upenn.edu](mailto:Frederick.Hitti@pennmedicine.upenn.edu)

immune system. While adjuvants have been utilized for decades, their mechanism of action is not entirely known. The Moderna and Pfizer/BioNTech COVID-19 mRNA vaccines stimulated a protective immune response with LNP acting as an adjuvant.<sup>2</sup> This adjuvant is novel in that it specifically induces a CD4<sup>+</sup> T cell helper response that stimulates antibody production, maturation, class switch, and long-term memory, known as T follicular helper cells.

Most who are reluctant to receive the vaccine cite safety concerns; however, some remain nihilistic about vaccine efficacy. The Pfizer/BioNTech vaccine demonstrated 95% efficacy and the Moderna vaccine showed similar efficacy as well.<sup>3,4</sup> While the long-term durability of protection is not definitively known, booster doses could be given in the future if necessary. The SARS-CoV-2 virus, like other members of the coronavirus family, has the capacity to mutate and evolve. Indeed, new strains of the virus have been observed.<sup>10</sup> Although the virus has the capacity to mutate to evade our immune system, data have shown that an immune response to one strain of the virus can neutralize other viral strains.<sup>10</sup> These data, coupled with the fact that immune responses to a vaccine will likely produce polyclonal antibodies, support efficacy of the vaccine despite viral mutations.

Another concern expressed by some is that the development and FDA review of the vaccines occurred too quickly for the vaccines to be adequately vetted. The development and review of these vaccines has been undeniably fast. The rapid development of the vaccines was possible due to the nature of mRNA vaccine production and the many years of preclinical and clinical development. All that is required for development is knowledge of the sequence of the antigen, in this case, the SARS-CoV-2 spike protein. Following their development, these vaccines underwent the same FDA review steps that all drugs are required to go through. The review process was quicker than normal due to the urgency of this pandemic. No steps were omitted in this process.

A greater understanding and acceptance of mRNA vaccines among the medical community is essential for widespread acceptance and utilization of these vaccines among

our patients. In the rapidly evolving field of medicine, it is our collective responsibility to educate each other and our patients about novel therapeutics.

Frederick L. Hitti, MD, PhD<sup>a</sup>

Drew Weissman, MD, PhD<sup>b</sup>

<sup>a</sup>Department of Neurosurgery

<sup>b</sup>Department of Medicine,

University of Pennsylvania,

Philadelphia

## References

1. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines—a new era in vaccinology. *Nat Rev Drug Discov* 2018;17(4):261–79.
2. Pardi N, Hogan MJ, Naradikian MS, et al. Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. *J Exp Med* 2018;215(6):1571–88.
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383(27):2603–15.
4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(5):403–16.
5. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics* 2017;9(2):12.
6. Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase I randomized clinical trials. *Vaccine* 2019;37(25):3326–34.
7. Zaks T. Emergency Use Authorization (EUA) application for mRNA-1273. Available at: <https://www.fda.gov/media/144583/download>. Accessed December 28, 2020.
8. Food and Drug Administration (FDA). Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. Available at: <https://www.fda.gov/media/144434/download>. Accessed December 28, 2020.
9. Food and Drug Administration (FDA). Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020. Available at: <https://www.fda.gov/media/144245/download>. Accessed December 28, 2020.
10. Baric RS. Emergence of a highly fit SARS-CoV-2 variant. *N Engl J Med* 2020;383(27):2684–6.