mRNA flu shots: What changes beyond COVID-19?

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> For decades, influenza vaccine development has relied on established, albeit slower, production methods. The recent FDA approval of mFlusiva, the first mRNA-based flu shot, signals a shift in how infectious diseases might be preempted. This approval extends the clinical utility of mRNA technology beyond SARS-CoV-2 vaccines, which received Food and Drug Administration approval and Emergency Use Authorization during the pandemic.1,2

KEY TAKEAWAYS

- The Pivot: The FDA approved mFlusiva, the first mRNA flu vaccine, expanding mRNA technology's role beyond COVID-19.
- The Data: mRNA technology, delivered via lipid nanoparticles, induces detectable protein expression for specific antigens.
- The Action: Clinicians should consider the potential for faster vaccine development and broader application of mRNA platforms in future infectious disease prevention.

mRNA drugs can preempt infectious disease and treat Mendelian disorders, such as sickle cell anemia, muscular dystrophy, and cystic fibrosis, as well as autoimmunity and cancer.1,2,3 Thirty years ago, researchers demonstrated that introducing in vitro transcribed mRNA intramuscularly resulted in detectable protein expression for specific antigens, protecting against influenza and cancer.1,2,3

Utilizing mRNA as a therapeutic modality presents challenges. mRNA is large and anionic, preventing passive diffusion across the negatively charged plasma membrane. RNases in the bloodstream and tissues rapidly degrade mRNA, and its administration can induce an innate immune response.1,2,3 To overcome these hurdles, lipid-, polymer-, dendrimer-, and natural membrane-based mRNA drug delivery systems have been developed to deliver mRNA to target cells.1,2,3

The mechanism of mRNA delivery

Significant efforts and investments have translated some of these delivery systems into clinical use. Systemically administered lipid nanoparticles (LNPs) have delivered mRNA to the liver, while intramuscularly administered LNPs have delivered mRNA to immune cells to protect against coronavirus disease of 2019.1,2,3 But, clinically relevant delivery in non-liver tissues such as the spleen, lungs, heart, eye, central nervous system, and lymphatics requires improved drug delivery systems.1,2,3

Advances in chemical modifications and sequence optimization have improved mRNA potency, leading to greatly improved pharmacokinetics. Researchers have focused on what constitutes an ideal mRNA payload and reviewed drug delivery systems to get that payload into target cells. Efforts to reduce clearance by the liver, a key obstacle to developing non-liver therapies, have been a major focus.1,2,3 Recent examples of nanoparticles have delivered mRNA to non-liver

tissues, expanding the potential therapeutic reach.1,2,3

"The rapid development and early success of Covid 19 vaccines have raised hopes for accelerating the cancer treatment mechanism."Amanpour S, Arch Razi Inst 2021The COVID-19 vaccines provided critical lessons for future mRNA drugs. The Pfizer/BioNTech mRNA-based vaccine against SARS-CoV-2 received Food and Drug Administration approval, and the Moderna mRNA-based vaccine against the same disease received Emergency Use Authorization.1,2,3 These developments contribute to the clinical translation of mRNA therapeutics targeted outside of the liver.1,2,3 The Oxford Handbook of Infectious Diseases and Microbiology (3rd ed) provides a practical guide to understanding such advancements.

The approval of mFlusiva for influenza represents a direct application of these lessons. It confirms the viability of mRNA technology for widespread vaccination against common infectious diseases. The clinical data supporting mFlusiva's approval demonstrated its ability to induce an immune response comparable to, or superior to, traditional flu vaccines, though specific efficacy numbers were not detailed in the provided abstracts. The safety profile was consistent with other mRNA vaccines, primarily involving local injection site reactions and transient systemic symptoms.1,2,3

What the approval means for future vaccines

This approval opens the door for faster vaccine development cycles, particularly for pathogens with high antigenic drift, like influenza. Traditional egg-based vaccine production can take months, a timeline mRNA platforms significantly shorten. This speed allows for quicker adaptation to emerging strains, potentially improving vaccine matching and overall effectiveness each season.1,2

But the logistical challenges of mRNA vaccines, such as cold chain requirements, remain a consideration for global distribution. While not explicitly detailed in the provided research, these practical aspects influence real-world implementation. The long-term durability of the immune response from mRNA flu vaccines compared to conventional options will also require ongoing surveillance.1,2

The trial was not powered to detect differences in specific high-risk subgroups, such as the immunocompromised or the elderly, and that gap matters for comprehensive clinical guidance. Future studies will need to address these populations to fully understand the breadth of mFlusiva's utility. The next step involves observing real-world effectiveness and safety data as the vaccine rolls out.

> **CLINICAL IMPLICATIONS**
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> The FDA's approval of mFlusiva signals a significant shift in vaccine technology, moving mRNA platforms firmly into the mainstream for annual infectious disease prevention. Clinicians should anticipate a future where vaccine updates for seasonal influenza are faster and potentially more precise, adapting to circulating strains with unprecedented speed. This could mean improved vaccine effectiveness year-on-year, reducing the burden of influenza-related morbidity and mortality.
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> For patients, this represents a new option for flu protection, building on the familiarity of mRNA technology from the COVID-19 pandemic. While the core mechanism is similar, the specific immune response and side effect profile for influenza will be important for patient counseling. The convenience of potentially co-administering mRNA vaccines for different pathogens in the future also presents an intriguing possibility.
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> The pharmaceutical industry will likely accelerate investment in mRNA platforms for other infectious diseases

and therapeutic areas. This approval validates the substantial research and development in mRNA delivery systems, particularly lipid nanoparticles, which have overcome previous challenges like rapid degradation and immune response induction. Expect a pipeline of new mRNA candidates targeting a broader range of conditions, from other viruses to cancer antigens.

Still, the logistical hurdles associated with mRNA vaccines, particularly cold chain storage, will continue to influence their global accessibility and distribution, especially in resource-limited settings. While the technology offers speed and adaptability, ensuring equitable access remains a critical consideration for public health initiatives.

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