Global Influenza Initiative

InFluNews

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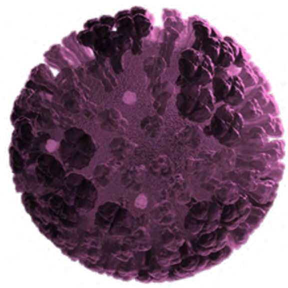

Welcome to the latest issue of InFluNews with this month's guest editor, Béhazine Combadière. Béhazine Combadière is a director of research at INSERM (Institut national de Santé et de Recherche Médicale) and head laboratory "Skin, Immunity and Vaccination" at the Center for Immunology and Microbial Infections (CIMI-Paris, France).

The rapid development of vaccines against COVID-19 has been instrumental in helping us fight the disease. Two of the first to be developed were messenger RNA (mRNA) vaccines.[1,2] But what are mRNA vaccines and what are the implications of this alternative approach to traditional methods of vaccine development in other disease areas such as influenza? In this edition of InFluNews we unravel the promise and challenges of mRNA vaccines.

What are mRNA vaccines and how do they differ from other vaccine technologies?

Unlike other vaccine types, mRNA vaccines use synthetic mRNA to direct protein synthesis in cells to produce a harmless component of a target germ (virus or bacteria), such as a viral spike protein. This informs the body's immune system to respond to the germ protein.[3–5]

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH

mRNA VACCINES: A NEW HOPE FOR INFLUENZA PREVENTION?
Can the promise of mRNA vaccines deliver for influenza what they have done for COVID-19?

Types of vaccines and their key features[5–7]

Vaccine type	How they work	Key features	Used to protect against
mRNA	Direct production of germ proteins to trigger an immune response	• Short development and manufacturing times • No risks of causing disease • Need to be refrigerated	COVID-19
Live, attenuated	Use a live, weakened version of the germ to trigger an immune response	• Strong and long-lasting immune response • Can confer lifelong protection • High-risk patients, such as those with weakened immune systems, should talk to their health care provider before receiving them • Need to be refrigerated	MMR Rotavirus Smallpox Chickenpox Yellow fever
Inactivated	Use an inactivated version of the germ to trigger an immune response	• Do not provide as much immunity as live vaccines • May require booster shots to confer ongoing protection • Require adjuvants	Hepatitis A Influenza Polio Rabies
Subunit, recombinant, polysaccharide or conjugate	Use specific parts of a germ (e.g. protein, sugar, capsid) to trigger an immune response	• Strong and targeted immune response • Can be used in patients with weakened immune systems or long-term health problems • May require booster shots to confer ongoing protection • Require adjuvants	Hib Hepatitis B HPV Whooping cough Pneumococcus
Toxoid	Use a toxin made by the germ to trigger an immune response	• Creates immunity specifically targeted to the disease-causing parts of the germ • May require booster shots to confer ongoing protection	Diphtheria Tetanus
Recombinant viral vector	Use a harmless modified version of a different virus encoded with part of the germ to trigger an immune response	• Can be developed rapidly • No risk of causing viral infection	COVID-19 Ebola

What are the advantages of mRNA vaccines?

mRNA vaccines offer a range of benefits over other vaccine types. These can be broken down into three main categories: safety, vaccine delivery and manufacture. We will take a closer look at each of these in more detail.

A minimal risk to patients

As mRNA vaccines do not use a live virus, there is no risk of infection or mutation.[4,8] What's more, these vaccines can be modified to reduce immunogenicity in order to further improve their safety profile.[9]

Following a series of unverified social media posts, a common concern about mRNA vaccines among patients is whether it can interfere with their DNA.[10] As mRNA does not enter the nucleus, it is unable to access or interfere with the DNA within a cell. The vaccine mRNA does not remain within the cell for long either as it is degraded through normal cellular processes.[4]

An efficient delivery system

Modifications made within the mRNA vaccine make it stable and highly translatable by the cell's natural protein-synthesising mechanisms. Furthermore, packaging of mRNA into carrier molecules, facilitates rapid and efficient uptake and expression within the cell cytoplasm.[8]

Unlike vector vaccines, mRNA vaccines do not have the potential to generate anti-vector immunity, which therefore allows for repeat dosing.[8]

Heterologous prime-boosting – in this case, the administration of two different vaccines expressing the same germ target – may be a useful strategy to deal with vaccine supply shortages or changing recommendations.[11,12] However, in a recent study published in The Lancet, heterologous vaccine schedules including the Pfizer-Biontech mRNA vaccine were shown to induce greater systemic reactogenicity following the booster dose than a homologous approach.[12]

A scalable manufacturing process

Due to high yields of *in vitro* transcription reactions used to make mRNA vaccines, they can be rapidly produced, are relatively inexpensive to manufacture and can be scaled up.[4,8]

Six disadvantages of mRNA vaccines

As promising as the benefits may sound, mRNA vaccines also come with a number of different challenges that need to be overcome:

1. **Expensive raw materials.**[13]
2. **Side effects.** There have been a large number of systemic and local reactions, as well as cases of myocarditis reported.[13,14]
3. **Instability at warm temperatures.** Some mRNA vaccines require cold temperatures to preserve the integrity of the mRNA resulting in potential cold chain storage issues.[13]
4. **Two-dose regimen usually required** to provide immunity which can be impractical in certain settings.[13]
5. **Vaccine hesitancy.** Some patients are reluctant to have the vaccine due to its genetically-engineered nature and the likelyhood of side effects.[10,13]
6. **Unknown duration of protection.**[15] Although the duration of protection from mRNA vaccines is not yet known, the level of neutralising antibodies may help to provide an indication of protection, as it has done with other vaccine types.[16]

Are any mRNA vaccines for influenza in development?

Two main approaches are currently being used in the development of mRNA vaccines against influenza:

- Non-replicating mRNA vaccines which just encode the germ protein of interest.[8,17]
- Self-amplifying mRNA which, in addition to the germ, also encodes viral replication machinery enabling intracellular RNA amplification and abundant protein expression.[8,17]

Moderna are currently developing a non-replicating mRNA vaccine as well as a combined COVID-19 + influenza vaccine.[15,17] Other manufacturers developing mRNA influenza vaccines include CureVac, EpiVax and Translatebio/Sanofi.[17,18]

Four ways in which mRNA vaccines could be beneficial for influenza control

1. The ability of mRNA vaccines to be produced rapidly means that they could potentially be adapted to target any new strains of influenza.[13]
2. In theory, there is potential for a 'universal' influenza vaccine that would work against any strain without the need for annual reformulations.[13]
3. The ability to incorporate different target germs could lead to the development of multi-disease vaccines.[13]
4. With the efficacy of COVID-19 mRNA vaccines shown to be similar between age groups, these vaccines may be a good candidate for older patients, who are naturally at greater risk from influenza.[19]

Key challenges to overcome with mRNA vaccines in order to make a difference in influenza

Resolve the temperature-sensitive stability issues of mRNA vaccines to make them more suitable for use in developing countries and regions with high temperatures.[13] Curevac and Suzhou Abogen Biosciences are working to resolve these issues.

Minimise side effects in order to increase acceptancy and uptake.[13,14]

Gain acceptance and uptake outside of COVID-19. While this novel technology has been adopted under the exceptional circumstances of COVID-19, uptake may be slower for other infectious diseases such as influenza.

Deliver protection against multiple strains

Prove to be effective and safe in those with pre-existing immunity

Demonstrate potential use as a universal influenza vaccine

Deliver durable immunity in the elderly

Prove to be effective and safe when delivered as a combination vaccine e.g. SARS-CoV-2 and influenza

Future perspectives: How might the vaccine landscape change following the success of mRNA SARS-CoV-2 vaccines?

We asked our guest editor, Béhazine Combadière, about her thoughts on the future of mRNA vaccines. "I believe that with the lower efficacy of inactivated vaccines, we may see a greater shift towards the development of mRNA vaccines that are designed to protect against multiple strains of influenza in the future." She went on to explain: "If we start to see some strains, such as H3N2, disappear, it could open up the vaccine landscape to the possibility of eradicating influenza forever." Underlining the important role of mRNA vaccines in the future, she concluded: "The development of multiple strain mRNA vaccines for use in animals and humans needs to be a future health priority."

GII summary statement

The speed at which vaccines against SARS-CoV-2 have been developed and licensed to fight the global COVID-19 pandemic is unprecedented. This has also provided an opportunity for new technologies, such as mRNA vaccines, to be applied to the prevention of infection and disease caused by other pathogens. mRNA vaccines against influenza are already in development and show the potential to solve some of the current challenges for influenza prevention, such as the need for a universal vaccine and the ability to combine vaccines for different pathogens, such as influenza and SARS-CoV-2. Multiple strain mRNA vaccines could potentially be used to benefit both animals and humans. The hope is that the extensive learnings on the development and administration of effective mRNA vaccines against SARS-CoV-2 can lead to improved strategies for influenza prevention in the near future.

About the GII

The GII is a global expert scientific forum that includes international scientists, researchers and clinicians with expertise in epidemiology, virology, infectious diseases, immunology, health economics, public health, primary care and geriatrics.

The GII receives financial support from Sanofi Pasteur which covers the involvement of Ogilvy Health, a medical communications agency which acts as a secretariat for the GII as well as coordinating logistics for the annual meeting, managing other GII projects and offering strategic counsel.

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