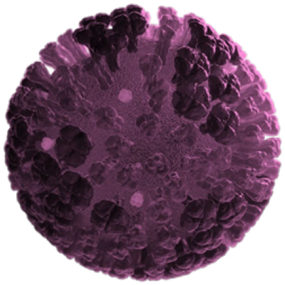
Global Influenza Initiative

InFluNews



The monthly newsletter from the Global Influenza Initiative (GII)

FEBRUARY 2022 | ISSUE 1

Welcome to the first issue of InFluNews for 2022 with this month's guest editor, Béhazine Combadière.

InFluNews was launched in March 2021. Since then, we have brought you the latest news on influenza and key developments during the COVID-19 pandemic, with topics ranging from the impact of the pandemic on influenza circulation, to mRNA vaccines through to preparing for future flu seasons.

*This month we have also launched our new **GII LinkedIn page** where you will find more information about the GII and its activities. If you missed any of last year's editions of InFluNews you can find them here.*

Advances in influenza vaccine technology

In this issue we provide a digest of key developments in influenza vaccine technologies, with a focus on novel vaccine platforms and vaccine delivery systems in development.

Introduction

A Research and Development (R&D) roadmap for influenza vaccines published in 2021 describes the need for improved influenza vaccines both to address seasonal influenza and to provide a rapid and effective response to future influenza pandemics.[1] Three critical limitations for seasonal influenza vaccines were highlighted: vaccine effectiveness – particularly in the elderly, variable effectiveness from year to year and long production times.[1] In this issue of InFluNews we focus on recent advances that aim to address some of these limitations.

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH:

Influenza vaccine technologies

An overview of key technologies being used in influenza vaccine development

Future influenza vaccines

What do we need and expect from future influenza vaccines?

Novel vaccine platforms

Three types of influenza vaccines are currently licensed in different countries; inactivated, live attenuated and recombinant HA vaccines. However, there is need for improved influenza vaccines which can provide broader and longer-lasting immunity against everchanging influenza viruses. There are a number of influenza vaccines in development that make use of novel vaccine platforms such as DNA, viral vectors and RNA, in order to try to address some of the limitations of established vaccines.

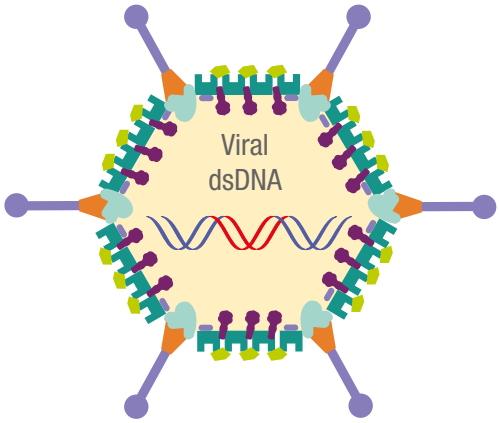
DNA vaccines

Advances which have enabled the successful development of DNA vaccines for human use include improvements in DNA transfection techniques, and the use of adjuvants to boost vaccine immunogenicity. DNA vaccines in clinical trials include those against SARS-CoV-2, Ebola, SARS, MERS, Lassa Fever, Zika, HIV and HPV,[2] and the first SARS-CoV-2 DNA vaccine has now been licensed by the Indian pharmaceutical company, **Zydus Cadila**.[3]

Multiple clinical trials involving influenza DNA vaccines are underway, including those designed to evaluate seasonal, pandemic and avian influenza vaccines. Various strategies are being tested for their potential to ameliorate influenza DNA vaccine immunogenicity, these include different routes of immunisation and heterologous prime-boost strategies. A Phase I trial studied the use of a trivalent HA DNA prime followed by trivalent inactivated influenza vaccine boost and compared administration via intradermal (ID) and intramuscular routes. All vaccination regimens studied were found to be safe and tolerable, with the ID route showing higher antibody titres.[4] The National Institute of Allergy and Infectious Diseases have completed a Phase I trial which includes the evaluation of a prime-boost strategy involving an HA Ferritin vaccine and an influenza DNA vaccine.[5,6]

Viral vector vaccines

Viral vector vaccines use an unrelated, non-pathogenic, viral backbone to deliver the target vaccine antigens.[7] Viral vector types include RNA (retrovirus and lentivirus), adenovirus and adeno-associated virus vectors.[8] Prior to the COVID-19 pandemic, only one viral vector-based vaccine had been licensed for use in humans against Ebola virus.[7] Two viral vector COVID-19 vaccines are now licensed for emergency use in many countries and multiple other COVID-19 viral vector vaccines are in development.[9]

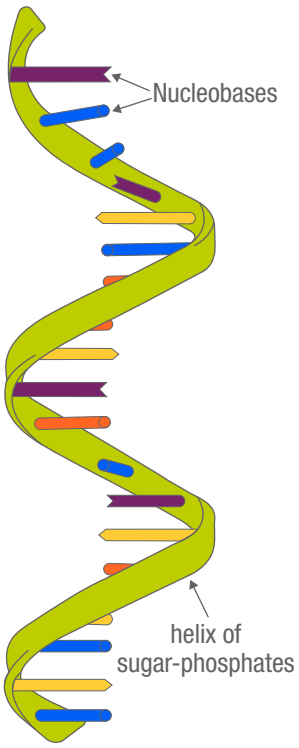


Adenovirus structure

An adenovirus-vector vaccine, VXA-A1.1, is among the more advanced of the viral-vector influenza vaccines in development. VXA-A1.1 is an oral tablet manufactured by **Vaxart, USA** that has completed Phase II trials and for which cellular correlates of protection were recently identified.[10]

RNA vaccines

The COVID-19 pandemic has accelerated the development of mRNA vaccine platforms, which are also being used to develop influenza vaccines. **Moderna**, **Pfizer** and **Sanofi/ Translate Bio** vaccines have all commenced clinical trials, while a **GSK/Curevac** vaccine is in preclinical trials. Moderna released Phase I study results on their quadrivalent mRNA influenza vaccine, mRNA-1010, in December 2021.[11] The antibody responses achieved were described as being generally on a par with standard (Sanofi) flu vaccines.[12] Interim Phase II study data are expected in early 2022.[11]



RNA
Ribonucleic acid

Sanofi/Translate Bio launched a Phase I/II study with two formulations of their monovalent mRNA vaccine (MRT5400 and MRT5401) in June 2021.[13] Interim results were positive, with 91 to 100% of study participants demonstrating neutralising antibody seroconversion, 2 weeks after the second vaccine dose.[14] A **Pfizer** Phase I study involving monovalent and bivalent modified mRNA influenza vaccines in older adults commenced in late 2021.[15] The **GSK/Curevac** lipid nanoparticle mRNA influenza vaccine CV7301 has shown strong and durable immune responses in preclinical trials to date;[16] the results of clinical trials are awaited to determine whether similar immune responses are seen in human populations.

Advances in vaccine adjuvants

Adjuvants are substances that are added to vaccine antigens to enhance the immune response in order to achieve stronger and longer-lasting protection.[17] Adjuvants used in licensed human influenza vaccines in different areas include aluminium salts, oil-in-water emulsions (MF59, AS03, and AF03), virosomes and heat-labile enterotoxin.[18] Newer types of adjuvants allow immune responses to be tailored towards a desired outcome; examples include monophosphoryl lipid A (MPL) and aluminium hydroxide in licensed vaccines against hepatitis B and human papillomavirus, and aluminium and CpG oligodeoxynucleotide in a malaria vaccine.[8] Both of these adjuvant types include Toll-like receptor (TLR) ligands. TLRs are a family of receptors that constitute the first line of defence against pathogens. The binding of ligands to TLRs activates intracellular signalling cascades that initiate the host's immune response – known as 'innate' immunity.[19] Adjuvants based on TLR ligands have a similar effect. Several different TLR agonists are being evaluated as influenza vaccine adjuvants in early clinical trials. They include TLR3 (rintatolimod), TLR4 (e.g. monophosphoryl lipid A), TLR5 (flagellin), TLR7/8 (imiquimod) and TLR9 (CpG oligodeoxynucleotide) agonists.[17] Other adjuvants in early clinical development include CAF01, a liposomal adjuvant and C-type lectin ligands.

Advances in vaccine delivery systems

Particle-based delivery systems are being used across different vaccine platforms. They are used to increase the immunogenicity and stability of subunit vaccine antigens.[20] A wide range of particle-based formats, including lipid nanoparticles, virus-like particles, protein nanoparticles, micelles, liposomes and polymeric nanoparticles, are currently being evaluated for COVID-19 vaccine candidates in preclinical and clinical trials.[20]

There are currently three types of particles that are components of influenza vaccines in clinical trials:

Virus-like particles (VLPs)

VLPs are a type of nanoparticle that can present vaccine antigens on their surface.[20] They are produced in such a way that the viral capsid antigens self-assemble and mimic the structure of authentic viruses, but do not contain the viral genome. They are therefore immunogenic and have an improved safety profile in comparison with live vaccines.[7,21] Approved VLP vaccines include those against human papillomavirus, hepatitis B and malaria. Meanwhile, both seasonal and pandemic influenza vaccines are being developed by **Medicago** and **Novavax**, with both seasonal vaccines in Phase III clinical trials.[22]

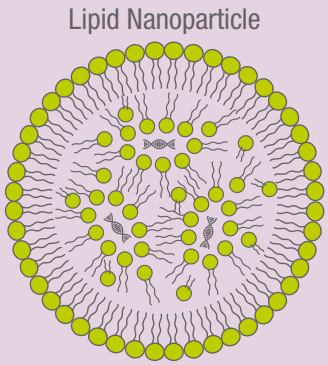
Lipid nanoparticles (LNPs)

LNPs are a type of nanoparticle that deliver vaccine antigens or nucleic acids by encapsulating them within their core.[20] Most recently they have been used to deliver mRNA in both the **Moderna** and **Pfizer** licensed COVID-19 vaccines where they act by preventing mRNA degradation and facilitating the delivery of the mRNA into the cell by endocytosis.[20] The **Novavax** licensed COVID-19 vaccine uses nanoparticle technology in its proprietary adjuvant, Matrix-M™, which consists of the adjuvant *Quillaja saponins* formulated with cholesterol and phospholipids.[23]

LNPs are also being used for influenza vaccines in development, including the **Moderna** vaccine that is in Phase I trials,[24] one of the formulations being tested by **Sanofi / Translate Bio**, also in Phase I[13] and the **Novavax** recombinant protein influenza vaccine which also uses the Matrix-M™ technology and has reached Phase III trials.[24,25]

Self-assembling protein nanoparticles

Ferritin, an iron-storage protein, is one example of a type of molecule that has the ability to self-assemble into nanoparticles. A SARS-CoV-2 S ferritin nanoparticle vaccine is in clinical trials[20] and a novel influenza H2HA-Ferritin nanoparticle vaccine has completed Phase I trials where it was shown to be safe and immunogenic.[6]



Nanoparticles

Nanoparticles are any particles of a nanoscale, i.e. with a size of 1–100nm.

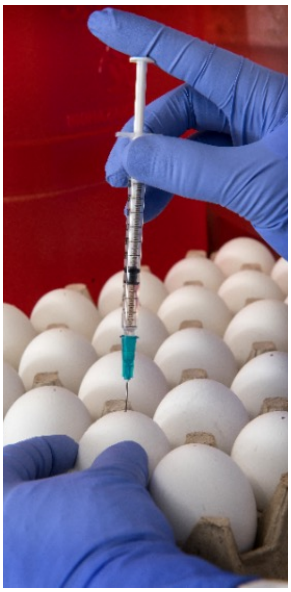
In the context of vaccines, they have been defined as '*nanoscale-sized and tunable particulate structures that mimic structural features of natural viruses*'.[20]

Progress in non-egg-based influenza vaccine technologies

Cell-culture-based vaccines

The aim of cell-culture-based influenza vaccines is to replace egg-based virus manufacture and its associated challenges, such as the substantial lead time required to manufacture virus by this method, the need for specific-pathogen-free eggs and the possibility of allergy to egg proteins in the vaccine recipient.[24]

Currently two manufacturers are producing cell-culture-based influenza vaccines; **Seqirus Limited** who produce Flucelvax® Quadrivalent and **SK Vaccines** who produce SKYCellflu Trivalent and Quadrivalent.[24] A key recent development in this field is the ability to use cell-derived seed viruses, which generally avoids the mutations that occur with egg-grown virus and produces virus that is antigenically more similar to viruses in circulation. A disadvantage of growing virus in cells is that virus titers are lower than those in eggs, resulting in low productivity and high cost.[17]



Influenza virus culture in eggs
(Image from CDC/James Gathany)

A recent review suggests that overall, cell-based vaccines are well-tolerated in adults, but evidence regarding their effectiveness compared with traditional seasonal influenza vaccines is limited.[26]

Recombinant protein-based vaccines

Recombinant protein-based vaccines include protein antigens that have been produced in a heterologous expression system, such as bacteria, yeast or insect cells. Key advantages of recombinant protein vaccines include that they are well-established, non-replicating and lack any infectious components and are therefore considered to be a safer approach than vaccines derived from live viruses.[27] Currently the only recombinant protein-based influenza vaccine registered worldwide is FluBlok™ (licensed as Supemtek® in the EU) manufactured by **Sanofi**. FluBlok™ is the first licensed vaccine to use an insect cell expression system and thus avoids the limitations of cell-culture vaccine production. Several other vaccines are either undergoing or have completed late-stage trials.[24]

Novel approaches in this area include those directed towards the design of a universal vaccine that requires an antigenic target that is conserved across human and zoonotic influenza strains. Candidates that have reached clinical trials include the conserved stalk domain of the HA antigen and the viral nucleoprotein.[28] Other novel approaches include a vaccine produced in plants (Phase II, **Medicago**, Canada)[29] and a vaccine that uses lipid nanoparticle technology, as described above (**Novavax**, USA).[24]

Future influenza vaccines

Several areas have been identified that should be addressed in order to improve the effectiveness of the influenza vaccines of the future:

1. **Selection of the vaccine seed virus**
   Mismatch between vaccine antigens and circulating viral strains is a major cause of low vaccine efficacy. Computer modelling-based approaches may allow us to better predict the antigenicity of future virus strains.[17]

2. **Use of cultured cells instead of eggs for vaccine virus preparation**
   Efforts are underway to increase cell-based vaccine productivity by modification of the virus and amelioration of the cells in which it is produced.[17]

3. **Increasing the neuraminidase content of vaccines**
   Despite evidence that the neuraminidase (NA) protein can elicit protective antibodies, the NA content of inactivated vaccines is not quantified and is suboptimal.[17]

4. **Targeting T-cell immunity**
   The viral nucleoprotein (NP) is known to be the major target of the cytotoxic T-cell (CTL) response. Cellular correlates of protection were recently identified for an oral influenza vaccine. In addition, vaccines which stimulate CTLs are known to reduce disease severity and mortality.[10,17]

5. **Targeting different populations**
   It is thought that the use of vaccines tailored towards specific target populations may improve protection.[17]

6. **Development of novel classes of adjuvants**
   Several novel adjuvants have been developed that can be used to tailor immune responses to vaccines.[17] As outlined above, adjuvants being used in early clinical trials of candidate influenza vaccines include TLR ligands, CAF01, and C-type lectin ligands.

7. **Development of universal vaccines**
   The aim of a universal vaccine is to offer 'protection against all influenza A and B viruses, including seasonal viruses and existing or emerging zoonotic viruses with pandemic potential.'[1]

Guest editor Béhazine Combadière comments:

Suboptimal vaccine effectiveness is a critical limitation of licensed seasonal influenza vaccines. Novel influenza virus vaccines are necessary to reduce the burden of seasonal influenza and to respond to the unpredictable emergence of pandemic influenza. COVID-19 has taught us valuable lessons about the impact and potentially devastating health, social and economic effects of a global pandemic, but at the same time facilitated accelerated vaccine development and a rapid translation into clinical studies for SARS-CoV-2 and other vaccines, including those against influenza. Questions remain on these vaccines' safety, efficacy and ability to provide broad protection as well as a rapid response to future pandemics. Numerous influenza vaccines have now reached Phase I, II and III clinical studies and we have begun to address many of the challenges on our roadmap towards providing better protection against influenza viruses.

GII Summary Statement

Advances in vaccine technologies, such as the development of nucleic acid SARS-CoV-2 vaccines, have been highly visible during the COVID-19 pandemic. Advances are being made across different aspects of vaccinology, such as vaccine platforms, adjuvants and delivery systems, and have the potential to benefit many vaccines, including those designed to protect against seasonal influenza. There is still work to be done in several key areas to better inform effective influenza vaccine design. The Research and Development (R&D) roadmap for influenza vaccines (2021) provides valuable guidance on key areas of focus for influenza vaccine R&D, and helps to focus resources on finding solutions that will lead to improved seasonal and pandemic influenza vaccines in the future.[1]

Two issues of critical importance to the development of more effective influenza vaccines are vaccine-induced immunity and vaccine strain selection. A better understanding of immune correlates of protection would allow for more informed vaccine design, ensuring that vaccines are optimised to achieve the desired immune response through appropriate use of antigens, adjuvants, delivery systems and administration routes. Predicting which influenza strains will circulate in upcoming influenza seasons remains difficult and has a major impact on vaccine effectiveness. Computer modelling is being investigated as an alternative approach to predict circulating viral strains, while the development of effective universal vaccines could circumvent this major challenge.

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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