

Clinical Commentary Review

Update on Influenza Vaccines: Needs and Progress

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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Learning objectives:

1. To list the major obstacles facing influenza vaccine development efforts.
2. To recognize existing safety concerns with current influenza vaccines.
3. To understand the advantages and disadvantages of the different types of influenza vaccines currently under development.

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Influenza is an annual seasonal epidemic, and occasionally pandemic, respiratory disease that causes considerable morbidity and mortality worldwide. Despite the widespread availability of safe and effective vaccines since the 1950s, this virus continues to pose a significant public health threat. Variable and often weak vaccine effectiveness, antigenic drift and shift, and vaccine

hesitancy are some of the obstacles that must be overcome to control this disease. In this article, we briefly review current influenza vaccines, address safety concerns and the need for newer influenza vaccines of higher efficacy, and discuss efforts to create broadly protective, universal influenza vaccines. © 2021 Published by Elsevier Inc. on behalf of the American Academy of

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*Abbreviations used**HA- Hemagglutinin**LAIV- Live attenuated influenza vaccine**M- Matrix protein**M2e- The extracellular domain of matrix 2 protein**NP- Nucleoprotein**RIV- Recombinant influenza vaccine***Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)****Key words:** *Influenza; Epidemic; Pandemic; Respiratory disease; Influenza vaccines***INTRODUCTION**

Influenza is an annual seasonal, and sometimes pandemic, disease that infects persons of all ages globally. Based on data from 2010 to 2020, it is estimated that in the United States alone, 9 million to 45 million illnesses, 140,000 to 810,000 hospitalizations, and 12,000 to 60,000 deaths occur annually because of influenza.¹ Globally, the World Health Organization estimates that there are 1 billion illnesses, 3 to 5 million severe cases, and 290,000 to 650,000 influenza-related respiratory deaths each year.² Nonpharmaceutical interventions (eg, masking, social distancing, and hand hygiene) play a role in preventing influenza transmission, and it is likely that these factors played a role in the remarkably attenuated influenza seasons observed in both the Northern and Southern hemispheres during the coronavirus disease 2019 pandemic in the period 2020 to 2021. Historically, prevention of influenza has been largely accomplished through immunization against the virus, most recently incorporating A/H1N1, A/H3N2, B/Yamagata-like, and B/Victoria-like strains in the quadrivalent vaccine. Recommendations for what strains to include in the vaccine are made annually by the World Health Organization for both Northern and Southern hemispheres. In the 2020-2021 influenza season, an estimated 190 million doses of influenza vaccine were distributed in the United States, in part based on fears of a "twindemic" with severe acute respiratory syndrome coronavirus 2. In the United States, influenza vaccination is recommended for everyone aged 6 months and older annually. Seven different influenza vaccines have been approved for use in the United States for all ages 6 months and older.³ Currently, both egg-based and cell-based vaccines are widely available, as well as high-dose and adjuvanted vaccines for persons 65 years and older.

Critical to the use of vaccines to prevent influenza morbidity and mortality is vaccine safety and efficacy. In regard to safety, influenza vaccines have an excellent track record.⁴ Although self-resolving and transient local and systemic side effects occur, the most common severe adverse event associated with influenza vaccine is Guillain-Barre syndrome, but this occurs in only approximately 1 in 1,000,000 doses. Measuring efficacy or effectiveness is a moving target each season based on type of vaccine and the antigenic match with circulating influenza strains, as well as geographic location. Like many vaccines, there is also a gradient of protection against death and complications of infection such as cardiovascular and neurological events (myocardial infarction, stroke, etc), versus

hospitalization, and severe, moderate, mild, and asymptomatic infection.

To achieve higher rates of efficacy, while maintaining safety, significant research in the development of so-called universal and other novel influenza vaccine platforms is occurring, with the idea of minimizing or eliminating the need for annual viral strain changes in vaccine composition, and the associated varying efficacy. The purpose of this brief review was to examine the types and limitations of currently available influenza vaccines and review the current state of the development of novel vaccine types.

CURRENT VACCINES

Three main types of seasonal influenza virus vaccines against influenza A and B viruses are available at this time: parenteral (intramuscularly) inactivated influenza vaccines (IIVs), intranasal live attenuated influenza vaccines (LAIVs), and parenteral recombinant influenza vaccines (RIVs).⁵ These vaccines are designed to elicit neutralizing antibodies against the influenza hemagglutinin (HA) protein and, to a lesser degree, against neuraminidase.

The current influenza vaccines can be trivalent or quadrivalent. Trivalent vaccine (IIV3) contains influenza A/H1N1, A/H3N2, and 1 influenza B lineage, and quadrivalent vaccines (IIV4, RIV4, and LAIV4) contain influenza A/H1N1, A/H3N2, and 2 influenza B lineages. Inactivated vaccines (including whole virus, split virus, and subunit vaccines) induce both humoral and cell-mediated immune responses and are recommended for all persons 6 months or older. LAIVs induce strong serum and mucosal antibody and cytotoxic T-cell responses; however, it is recommended only for those aged 2 to 49 years and is not recommended for those with asthma or who are immunocompromised. RIVs are produced in mammalian or insect cells (without the use of embryonated chicken eggs) and offer many advantages, including quicker manufacturing and avoidance of egg-adaptative mutations.^{6,7}

For patients 65 years and older, vaccine formulations are available as high-dose (HD-IIV4 with an increased HA content) or containing an adjuvant (MF59). These formulations have demonstrated enhanced efficacy and a good safety profile.^{8,9} Vaccines are very safe, and the vaccine benefits immensely overcome the very minor risks of associated complications. Common local (eg, soreness, pain, and erythema) and systemic (eg, rash, headache, fever, urticaria, and myalgia) reactions are mainly mild and temporary, and vaccine-associated hypersensitivity reactions are very infrequent.^{10,11} The 1976-1977 A/New Jersey/76 swine influenza vaccine in adults was linked to an increased risk of Guillain-Barre syndrome, with estimated attributable risk of approximately 1 case per 100,000 vaccinations.¹² This association has not been observed since, and studies suggest that the risk of Guillain-Barre syndrome following influenza infection and illness is much higher than after influenza vaccination.¹³ Cases of narcolepsy (a complex chronic hypersomnia syndrome) were associated with the pandemic A/H1N1 influenza vaccination in the period 2009 to 2010 in several European countries where AS03-adjuvanted pandemic vaccine (Pandemrix) was used.^{14,15} Most individuals with narcolepsy after AS03-adjuvanted influenza A/H1N1 vaccine carry an HLA-DQB1*06:02 risk allele that seemed to regulate immune response against Pandemrix-derived nucleoprotein (NP).¹⁶ Better understanding of the genetic and nongenetic drivers of

TABLE I. Clinical trials of influenza vaccines

Universal vaccines					
Trial ID	Phase	Vaccine type	Sponsor	Country	Details
NCT03789539	1	Unknown	VA Pharma Limited	Russia	
NCT03275389	1	Inactivated virus + AS03 adjuvant	GSK	United States	Development to end after completion of the clinical trial
NCT03300050	1	Chimeric HA + AS03A adjuvant	PATH	United States	
NCT00921973	1	M2e protein + flagellin	VaxInnate Corporation	United States	Alone or with TIV
NCT00921947	1 and 2	M2e protein + flagellin	VaxInnate Corporation	United States	IM vs SC
NCT03450915	3	Peptide-based vaccine	BiondVax Pharmaceuticals	Poland	Development to end after completion of the clinical trials
NCT01265914	1	Peptide-based vaccine	Immune Targeting Systems Ltd	United Kingdom	
NCT04650971	1	Recombinant influenza virus - ΔNS1	Pharmenterprises Biotech LLC	Russia	
NCT00921206	1	M2e protein + flagellin	VaxInnate Corporation	United States	Prime-boost regimen
NCT03816878	1	Subunit vaccine	NIAID		
NCT02293317	2	Peptide-based vaccine	BiondVax Pharmaceuticals	Israel	M001 prime with TIV boost
NCT04441047	1 and 2	Allogeneic cellular vaccine	Immunovative Therapies Ltd	United States	
NCT01419925	2	Peptide-based vaccine	BiondVax Pharmaceuticals Ltd	Israel	In elderly volunteers
NCT01587131	1	DNA vaccine	Inovio Pharmaceuticals	Canada	
NCT01405885	1	DNA vaccine	Inovio Pharmaceuticals	United States	
NCT02691130	2	Peptide-based vaccine	BiondVax Pharmaceuticals	Hungary	M-001 primer with and without an H5N1 booster
NCT03180801		Peptide-based vaccine + Montanide ISA-51	PepTcell Limited	United Kingdom	Human challenge study
NCT01146119	2	Peptide-based vaccine	BiondVax Pharmaceuticals	Israel	
NCT02962908	2	Peptide-based vaccine + Montanide ISA-51	PepTcell Limited	The Netherlands	
Newer vaccines					
Trial ID	Phase	Vaccine type	Sponsor	Country	Details
NCT04785794	1	Inactivated virus	FluGen	United States	Intranasal, ages 50-85 y
NCT03999554	1	Inactivated virus	FluGen	United States	H3N2 components
NCT02822105	1	Inactivated virus	FluGen	United States	
NCT04960397	1	Inactivated virus	FluGen	United States	Prime-boost regimen
NCT03553940		Inactivated virus	FluGen	United States	Pediatric population
NCT03880474	2	MVA-based NP and M1 vaccine	Vaccitech	Australia	
NCT03883113	2	MVA-based NP and M1 vaccine	Vaccitech	Belgium	Human challenge study
NCT03300362	2	MVA-based NP and M1 vaccine	Vaccitech	Belgium	Combined with seasonal IIV
NCT04120194	3	Nanoparticle + Matrix-M adjuvant	Novavax	United States	
NCT01761123	1	Adenovirus vector, oral vaccine	Vaxart	United States	Oral capsule targeted to ileum
NCT03121339	1	Adenovirus vector, oral vaccine	Vaxart	United States	Oral vaccine in fasting adults ± dsRNA adjuvant
NCT01688297	1	Adenovirus vector, oral vaccine	Vaxart	United States	Dose ranging study in healthy adults
NCT02918006	2	Adenovirus vector, oral vaccine	Vaxart	United States	Cohort with low preexisting immunity to 2009 pandemic H1N1

IM, Intramuscular; NIAID, National Institute of Allergy and Infectious Diseases; SC, subcutaneous.

vaccine adverse events at the molecular level (the field of adversomics)¹⁷ would further benefit the development of current and next-generation influenza vaccines.

NEW VACCINES IN DEVELOPMENT

Historically, most influenza vaccines have been split virus vaccines containing predominantly the HA protein from selected

virus strains. More recently, subunit vaccines containing HA protein and intranasal vaccines containing cold-adapted, live, attenuated viruses have been added to the repertoire of vaccines.^{18,19} Candidate vaccines in preclinical development span the gamut of vaccine types. Inactivated virus and split virion formulations are being combined with novel adjuvants to improve immunogenicity and broaden reactivity. Vectored vaccines are also being explored. The success of mRNA vaccines

against coronavirus disease 2019 has opened up the possibility of nucleic acid vaccines for influenza, and indeed clinical trials have already begun.²⁰

The continuous antigenic drift of seasonal influenza viruses and frequent point mutations in the viral genome require reformulation of vaccines every 1 to 2 years to provide protection against circulating drifted strains. Overall, influenza vaccine effectiveness has varied from year to year and ranges from 40% to 60%.²¹ This demonstrates the importance of improving current influenza vaccines and developing universal influenza vaccines that enhance cross-protection. A great deal of effort is currently focused on developing these broadly protective universal influenza vaccines that are broadly protective. The National Institutes of Health has released 4 criteria for such vaccines: greater than or equal to 75% effective at preventing illness, elicit immune responses against both group I and II influenza A strains, provide protection that lasts at least 1 year, and are effective in all age groups.²² Existing platforms are largely viewed as inadequate to meet these goals. Several universal influenza virus vaccine candidates that target conserved regions of the influenza virus to induce broad protection against all influenza viruses are currently being developed and tested in clinical trials.²³ The universal influenza vaccines seek to move beyond antibody responses targeting the head of the HA protein, which are typically neutralizing but strain-specific to those targeting the HA stalk region, which are more broadly cross-reactive and maintain neutralizing activity. Other proteins, such as the extracellular domain of matrix 2 (M2e) protein, are also targeted for antibody responses—these are also cross-reactive, and although they lack neutralizing activity, they do mediate antibody-dependent cell-mediated cytotoxicity. In addition, a central feature of most universal influenza vaccines is the development of broadly cross-reactive T-cell responses to other viral proteins (eg, M1 and NP).²³ Innovation is also driving research into novel vaccine types, including nanoparticle-based vaccines, virus-like particle vaccines, peptide-based vaccines, and vectored vaccines. In fact, multiple clinical trials of various influenza vaccine types are underway or have been completed. A more complete review of these trials was published in October 2020.²⁴

Nucleic acid vaccines

RNA and DNA vaccines have a number of advantages over established vaccine formulations because they do not require passaging virus in eggs or cell lines. A recent report by Guilfoyle et al²⁵ found that a polyvalent DNA vaccine containing sequences for the NP, M, HA, and neuraminidase proteins from pandemic influenza strains elicited robust, cross-reactive immune responses and protected ferrets against a homologous challenge with A/California/07/2009 (H1N1)pdm09 as well as heterologous challenge with A/Viet Nam/1203/2004 (H5N1) (a strain not represented by any of the sequences in the vaccine).²⁵ Multiantigen RNA vaccines are also being tested in animal models.²⁶

Attenuated virus vaccines

Deletion of the NS1 protein was found to yield a safe and immunogenic, replication-deficient influenza virus.²⁷ A recent phase 1 clinical trial using this attenuated virus as a vaccine reported that recipients developed heterotypic cross-neutralizing antibody responses recognizing A/H1N1, A/H3N2, and A/H5N1²⁸ viruses.²⁹ Another influenza vaccine based on a similar Δ NS1

backbone has also completed a phase 1 clinical trial, but no data have yet been reported (see Table I). Yet another construct is the M2SR vaccine, which has a deletion in the M2 gene, enabling it to express a full complement of influenza proteins but not any infectious viral particles. Multiple clinical trials have been completed or are underway using M2SR backbones expressing various HA proteins (see Table I).³⁰

Vectored vaccines

Vaccitech has developed an MVA-based vaccine expressing the NP and M1 proteins that is currently in clinical trials. Similarly, adenoviral vectors containing HA proteins are being explored as platforms for influenza vaccines.^{31,32} An intranasally administered recombinant adenovirus expressing NP and M2 proteins is capable of generating protective immunity against both group 1 and 2 influenza A viruses, whereas similar constructs based on influenza B NP provides cross-reactive immune responses to multiple influenza B strains.³³ A vesicular stomatitis virus–vectored vaccine has also shown cross-protection against multiple H5H1 strains.³⁴ An adjuvanted adenovirus-based oral vaccine has undergone a number of clinical trials, including a human challenge study.^{35,36}

Nanoparticle vaccines

Nanoparticle platforms provide stable presentation/retention of the antigen at the injection site and/or targeted delivery to specific antigen-presenting cells. One such approach using double-layered nanoparticles containing M2e and headless HA proteins elicited robust humoral immunity and protected mice against heterologous challenges with divergent influenza A viruses.³⁷ Another nanoparticle product is NanoFlu, containing recombinant HA protein and the Matrix-M adjuvant, which has an ongoing phase 3 clinical trial as of July 2021.

Adjuvants used with influenza vaccines

A number of adjuvants are being used in influenza vaccines including alum, which creates a depot effect and also recruits innate immune cells to the injection site; MF59, an oil-in-water emulsion containing squalene, Tween 80, and Span 85, which activates monocytes, macrophages, and granulocytes, increases antigen uptake, and drives antigen-presenting cell differentiation/maturation and the secretion of chemokines, leading to enhanced lymphocyte recruitment; and AS03, another oil-in-water emulsion containing Tween 80, squalene, and α -tocopherol, which also promotes cell recruitment, antigen uptake and transport to the lymph node, and cytokine secretion. Influenza vaccines accompanied by a wide array of additional adjuvants, including Toll-like receptor ligands, nanoemulsions, immunostimulatory compounds, and cytokines, are currently being tested in clinical trials.¹⁸

CONCLUSIONS

Critical to highly effective vaccines that reliably prevent influenza infection and its complications is the development of vaccines that eliminate the need for closely matched antigenic viral strains each season. By virtue of the rapid mutation rate in influenza vaccines, vaccine efficacy and effectiveness vary across ages, geography and even within a given season. Thus, the development of vaccines that target highly conserved areas of the virus are a welcome advance. Vaccines that do not require annual administration will also reduce the complexity and cost of

influenza prevention programs such as universal influenza vaccines, and would likely increase vaccine coverage rates, leading to reduced illness, morbidity, and mortality. Much interest and research is occurring in the field of novel influenza vaccines. Such efforts are critical to protecting the public health and relieving the considerable annual morbidity and mortality attendant to annual epidemics and periodic pandemics. Further research and research funding are needed to make these promising efforts a reality.

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