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Improving influenza vaccines: challenges to effective implementation

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Influenza virus causes contagious respiratory illness and remains a major burden on healthcare systems and the economy. Seasonal influenza vaccine is the most cost-effective way to combat the disease. However, underestimation of disease severity and controversy over vaccine safety and effectiveness hampers public confidence in vaccination. Action is needed to restore public confidence and improve vaccine uptake. Tailoring seasonal influenza vaccines according to immune responsiveness and infection/vaccination history of different populations can improve vaccine efficacy and effectiveness. Steady progress has been made in next generation influenza vaccine designs aiming at broad and long-lasting protective immunity in pre-clinical and clinical studies. However, substantial research and regulatory effort is required before reaching the goal of a truly universal vaccine.

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Introduction

Influenza, 'flu', is a major respiratory illness caused by the influenza virus. Infection can lead to serious illness, fulminant pneumonia and death in all age groups. Globally the influenza viruses infect 5–10% of adults and 20–30% of children annually, resulting in up to 650 000 deaths [1••]. Vaccination is the most cost-effective prophylaxis to combat the disease. The World Health Organization (WHO) recommends annual vaccination for high-risk groups, that is, pregnant women, children under the age of five, the elderly and patients with chronic disease, along with occupational groups such as healthcare workers (Table 1).

Currently licensed seasonal vaccines are cost-effective and increased vaccine uptake would reduce morbidity and mortality in the general public, especially high-risk groups. Although the safety of licensed vaccines has been extensively studied and proven, misunderstanding of adverse events, especially some rare but serious cases such as narcolepsy, has triggered vaccine safety scares in the general public. The constant antigenic changes in influenza viral proteins create challenges in virus strain selection for annual seasonal vaccine manufacturing. Mismatch between vaccine viruses and novel circulating viruses greatly influences vaccine effectiveness, and thus hampers public confidence in seasonal influenza vaccines. In this review, we will look at both challenges and incremental steps to improving seasonal influenza vaccines and summarize some of the interesting next generation vaccines under development.

Influenza virus and licensed seasonal vaccines

Influenza virus is a member of the Orthomyxoviridae family with a segmented negative-sense single-strand RNA genome. There are four genera of influenza viruses, namely influenza A, B, C and D, circulating in natural hosts [2]. Influenza A and B viruses cause annual outbreaks or epidemics; influenza C infections are often asymptomatic or cause mild illness; Influenza D is not known to infect or cause illness in human. Influenza A and B virus genomes are composed of eight segments, encoding 10–17 proteins (Table 2) [3]. Influenza A virus can be further divided into subtypes based on the two major surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA). Influenza B virus are divided into two major lineages based on their HA. The nature of the error-prone viral RNA-dependent RNA polymerase and random reassortment of gene segments between influenza viruses lead to constant antigenic drift and occasional shift in HA and NA, and other viral proteins [4]. These antigenic changes cause annual outbreaks, epidemics and occasional pandemics, creating a challenge for global surveillance of circulating viruses and vaccine strain selection [5,6]. The WHO biannually recommends updating of the composition of vaccine strains, which contain influenza A/H1N1 and A/H3N2, together with

Table 1

The groups prioritized for influenza vaccination by the WHO

Risk group[a]	WHO reasoning for the recommendation
Pregnant women (Infants <6 months)	Increased risk of severe disease and mortality in mother and child, vaccinated mothers provide indirect protection to infant up to 6 months old, globally feasible, pregnant women have contact with health services
Healthcare workers	Increased occupational exposure, reduces morbidity and mortality among patients, protects integrity of healthcare system, feasible to implement
Children <2 years	Main burden of serious disease, greatest transmitters of virus, harder to implement
Children 2–5 years	Carry large burden of serious disease, respond better to vaccine than younger children and the elderly.
Elderly >65 years	Highest risk of mortality, important target group, but vaccine less effective in this group. Costly to conduct vaccination campaign.
Patients with chronic disease	Highest risk of severe disease, identification of individuals is resource intensive.

[a] Risk groups are in a prioritized order based on WHO position paper on influenza vaccines, the risk posed for each group, and the cost effectiveness and the feasibility of conducting vaccination in each group.

Table 2

The influenza A genome segments, proteins encoded and vaccine targets

Gene segment[1] (No. of nucleotides)	Protein (No. of amino acids[2])	Targeted in vaccine strategies
1 (2341)	PB2 (759)	Trace amount in whole and split IIV.
2 (2341)	PB1 (757)	Trace amount in whole and split IIV.
	PB1-F2	
	N40	
3 (2233)	PA (716)	Trace amount in whole and split IIV.
	PA-X	
	PA-N155	
	PA-N182	
4 (1778)	HA (565)	Main component in IIV, LAIV and recombinant-HA vaccine. HA-Head region: Targeted by COBRA. HA-stalk region: Targeted by Chimeric and headless.
5 (1565)	NP (498)	Low amounts in whole and split IIV[3] Targeted by MVA-NP + M1.
6 (1413)	NA (454)	Subdominant component in IIV and LAIV. Targeted by VLP-NA + M2e.
7 (1027)	M1 (252)	M1: Targeted by MVA-NP + M1.
	M2 (97)	M2: Targeted by VLP-NA + M2e.
	M42	
8 (890)	NS1 (230)	
	NS2 (121), also termed NEP	
	NS3	

[1] Adapted from: Shaw ML, Palese P. 2013. **Orthomyxoviridae.** *In Fields Virology, 6th Edition*. pp 1151–1185. Philadelphia: Lippincott Williams & Wilkins.
[2] Number of amino acids of each protein listed is from influenza A/Puerto Rico/8/1934 strain. The length of each protein varies among different strains and especially different subtypes.
[3] The amount of NP varies according to the different vaccines produced by different vaccine manufacturers.

the dominant influenza B lineage in circulation (trivalent) or both B lineages (quadrivalent) [7].

Current licensed influenza seasonal vaccines are available as inactivated, live attenuated, and recombinant-HA vaccines (Figure 1). Inactivated influenza vaccine (IIV) includes whole inactivated virus, split virion or subunit formulations and induces mainly strain specific serum antibodies against HA. Egg-based IIVs have been licensed in the US and Europe for decades for use in adults and children 6 months and older, with the MF59 adjuvanted or high dose vaccines licensed for use in the elderly [8•,9]. Cell-based IIV was licensed in the US and Europe (Hungary) for individuals allergic to eggs. Live attenuated influenza vaccine (LAIV) is licensed in the US and Canada (for use in adults and children 2 to 49 and 59 years old, respectively), Europe (for use in children and adolescents, 2–17 years of age), Russia and India [10]. The cold-adapted, temperature-sensitive viruses replicate in the upper respiratory tract to mimic natural infection. Hence, LAIV induces broader and multifaceted immune responses including antibodies in serum and the upper airway mucosa [11] and T cells [12,13]. In 2013, a recombinant-HA expressed in insect cells using baculovirus vectors (FluBlok) was licensed for use in adults aged 18–49 years old in the US [14,15]. This new vaccine