



Influenza vaccination: protecting the most vulnerable

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To protect the elderly from influenza, multiple strategies to overcome immunosenescence need to be utilised, such as improving vaccine efficacy, indirect protection via vaccinating children and healthcare workers, and developing a universal vaccine <https://bit.ly/30KXzYn>

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ABSTRACT Influenza virus infection causes seasonal epidemics and occasional pandemics, leading to huge morbidity and mortality worldwide. Vaccination against influenza is needed annually as protection from constantly mutating strains is required. Groups at high risk of poor outcomes include the elderly, the very young, pregnant women and those with chronic health conditions. However, vaccine effectiveness in the elderly is generally poor due to immunosenescence and may be altered due to “original antigenic sin”. Strategies to overcome these challenges in the elderly include high-dose or adjuvant vaccines. Other options include vaccinating healthcare workers and children as this reduces community-level influenza transmission. Current guidelines in the UK are that young children receive a live attenuated nasal spray vaccine, adults aged >65 years receive an adjuvanted trivalent inactivated vaccine and adults aged <65 years with comorbidities receive a quadrivalent inactivated vaccine. The goal of a universal influenza vaccine targeting conserved regions of the virus and avoiding the need for annual vaccination is edging closer with early-phase trials under way.

Introduction

Influenza is a virulent and contagious respiratory virus which causes annual disease outbreaks in temperate climates and sporadic spikes in prevalence within the tropics [1]. Local and global influenza outbreaks (epidemics and pandemics, respectively) carry a high mortality, morbidity and economic cost. Symptoms of influenza virus infection are classically fever, myalgia, headache, sore throat, dry cough and coryza. However, patients can present with a wide spectrum of disease including pneumonia, exacerbations of underlying lung disease, and extrapulmonary symptoms, affecting the gastrointestinal and neurological systems [2, 3]. Annually, influenza causes three to five million cases of severe illness and up to 650 000 deaths globally. Of these, ~100 000 deaths occur in children aged <5 years, and 120 000–240 000 deaths occur in people aged >75 years [1, 4]. Other populations at risk of severe morbidity and mortality are 1) pregnant women (particularly during the third trimester); 2) immunocompromised individuals; and

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3) those with multiple comorbidities [5–11]; the latter two risk factors are more common in older people. Seasonal influenza is estimated to reduce annual gross domestic product in the UK by 0.5–4.3% (GBP 8.4–72.3 billion) [12]. In the United States, the estimated annual direct medical costs of seasonal influenza were USD 3.2 billion [13]. Due to the morbidity, mortality and socioeconomic burden of influenza, worldwide public health strategies, namely annual influenza vaccination, focus their protection towards the most vulnerable populations [2, 14–16]. Additionally, given the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, it becomes increasingly important that elderly and vulnerable groups are protected against seasonal influenza. Furthermore, there are mounting concerns on the impact of co-circulating and interaction between SARS-CoV-2 with seasonal influenza. Although reports from Hong Kong showed a shortened influenza season with fewer cases, likely to be secondary to social distancing, face masks and improved hand hygiene, it is yet to be seen if this will be replicated in the upcoming European influenza season [17]. This review explores the utility of yearly influenza vaccination, its effectiveness in different groups, the effect of repeated vaccination, the development of the universal influenza vaccine and the role of indirect protection.

The influenza virus: varied, drifting and shifting

The influenza viruses are enveloped, single-stranded, negative-sense RNA viruses from the Orthomyxoviridae family with a segmented genome. There are four influenza subclasses: A, B, C and D [3, 18]. Of these, A and B are most clinically important. Influenza A and B viruses express two surface glycoproteins: haemagglutinin (HA) and neuraminidase (NA). HA enables attachment and fusion of the virus to host cells within the respiratory tract and NA allows the subsequent cleavage and release of the virus from host cells [18]. Influenza A subtype is described by the surface HA and NA antigens expressed. There are 18 known HA subtypes divided in two groups (1 and 2) and 11 NA subtypes [18]; these provide the name given to influenza A strains. For example, “swine flu”, which caused a pandemic in 2009 and now contributes to seasonal infections, is named H1N1. Such zoonotic influenza strains are of concern as potential causative pathogens in future epidemics or pandemics, in particular H5N7 and H7N9 [19]. Influenza B has two lineages in circulation: Victoria and Yamagata [2].

The high rate of mutations and genetic reassortment are key to the virus’s ability to cause seasonal epidemics and occasional pandemics. The influenza genome is segmented, which allows genetic material to be exchanged when two strains of influenza A virus infect the same host cell, in humans or in the extensive animal reservoirs including birds, pigs, horses and bats [3, 20–22]. This exchange changes the transcribed antigens, potentially producing a new subtype of influenza A to which humans are immune-naïve [3]. This process, called antigenic shift, has caused influenza pandemics. Antigenic drift provides another important mechanism for variation in influenza A and B viruses. During replication, there is a high frequency of point mutations to the HA gene. HA is often the target of adaptive immunity to the virus, and mutations to this gene alter the antibody binding site. This means that antibodies formed during previous infection may have a lower affinity, or are ineffective [3]. Antigenic drift and shift are key reasons that annual vaccination against currently circulating strains is required.

Influenza vaccine design and delivery

The composition of influenza strains in the vaccine is updated biannually based upon recommendations from the World Health Organization (WHO), which tracks clinical data on current and emerging strains during both the northern and southern hemisphere influenza seasons. This allows the production of a targeted vaccine, although further genetic alterations of the prevalent viral strains can result in a mismatch between circulating and vaccine strains, leading to poor vaccine effectiveness by the time vaccines are deployed. An example would be the 2017/18 trivalent vaccine which had a low effectiveness of ~25% in the UK due to mismatching of the predominant influenza A strain and lacking the circulating Yamagata strain [23].

Broadly, influenza vaccines come in two forms: trivalent (containing antigens of influenza A subtypes H1N1 and H3N2, and one of the two influenza B subtypes) or quadrivalent (containing strains of H1N1, H3N2 and both Victoria and Yamagata influenza lineages). Quadrivalent vaccines have been shown to reduce morbidity, mortality and healthcare service usage, compared to trivalent vaccination [24, 25]. The quadrivalent vaccine has been found to demonstrate an incremental cost-effectiveness ratio of £27 378 per quality-adjusted life-year *versus* nonvaccination [26, 27]. However, comparative cost-effectiveness of the extended vaccine *versus* trivalent vaccine is highly dependent upon the population burden of influenza B [28]. Both the quadrivalent and trivalent vaccine are available as a live attenuated influenza vaccine (LAIV) or an inactivated influenza vaccine (IIV). In the UK, the LAIV is used in children due to a more acceptable route of administration and an association with improved immune and clinical outcomes [29–31]. While IIV is administered intramuscularly, the LAIV is administered intranasally. The attenuated virus replicates within the mucosal tissues of the nasopharynx, mimicking physiological infection. LAIV

nasal administration leads to higher secretory IgA titres than intramuscular IIV [29]. While both vaccine delivery systems utilise humoral and cell-mediated immunity, there may be immunological benefit in imitating natural infection.

Annual influenza vaccine effectiveness in different populations

Vaccine effectiveness is often calculated using clinical prevalence of influenza-like illness (ILI) or laboratory confirmed influenza (LCI). However, challenges arise due to the wide range of viruses that cause ILI and a paucity of laboratory confirmation. Despite this, a recent systematic review and meta-analysis found that influenza-vaccinated populations demonstrated a 51% reduction in LCI-related hospitalisation rates in adults aged 18–65 years and a 37% reduction in those aged >65 years. As expected, years with greater antigenic variation between vaccine strains and circulating viruses had higher rates of hospitalisation, as the protection conferred was less effective [32].

A 2018 Cochrane review found similar protective effects. In 80 000 individuals enrolled in 52 clinical trials, vaccination reduced influenza rates in healthy adults aged 16–65 years from 2.3% to 0.9%. Vaccination also lowered the prevalence of ILI from 21.5% to 18.1%. However, due to the low overall population risk of influenza, the number of healthy adults needed to treat to prevent one case (NNT) of influenza and ILI were 71 and 29, respectively [33] (table 1).

Reviews of influenza vaccination in young children and the elderly were more encouraging. In children, LAIV reduced LCI from 18% to 4% and ILI from 17% to 12%, when compared to a placebo. This translates to NNT of only seven and 20, respectively. IIV reduced risk of influenza from 30% to 11% and ILI from 28% to 20%, in children (NNT of five and 12 for influenza and ILI, respectively) [34]. In the over-65s, the vaccine reduced the risk of influenza from 6% to 2.4% (risk ratio (RR) 0.42, 95% CI 0.27–0.66; NNT=30), and ILI from 6% to 3.5% (RR 0.59, 95% CI 0.47–0.73; NNT=42) in comparison to placebo [35].

Therefore, multiple studies employing different epidemiological techniques have demonstrated moderate effectiveness of influenza vaccination, with clearer benefits in key “at-risk” populations.

The problems with measuring vaccine effectiveness

Determining vaccine effectiveness is vital in constructing optimal public health strategies to protect those at risk from influenza. To assess the effectiveness of the influenza vaccine, multiple approaches and study designs have been used. Measuring haemagglutinin inhibition titres is one method, where titres >1:40 are traditionally linked with a 50% protection rate. However, recent studies have shown that these target titres are not accurate predictors of protection in children and the elderly, and often overestimate levels of protection [36, 37]. More recently, a different approach, the test-negative study design (TND), has been used to evaluate vaccine effectiveness. This adapted case–control method compares vaccination status of cohorts of patients presenting to primary care and other settings with influenza-like symptoms and whether or not they have LCI [38–40]. The advantages of TND are the reduction in disease misclassification (as cases are laboratory-confirmed), lack of reliance on possibly unreliable antibody titres, and that it may prevent the influence of health-seeking behaviour on data [38–40]. However, there are several disadvantages to TND. It requires cases to seek medical attention, which may not occur if symptoms are mild. Furthermore, it does not control for risk factors predisposing an individual to ILI [40]. These limitations mean that TND can underestimate the effectiveness of vaccines. Due to these disadvantages, recent Cochrane reviews have omitted studies that use this design [38]. Therefore, issues remain with methodology and data collection in clinical trials investigating influenza vaccines, and these issues may hamper public health strategy.

TABLE 1 Summary of the number needed to treat (NNT) with the influenza vaccine in different age groups to protect against influenza

	NNT against influenza	Relative risk (95% CI)
Age 3–16 years (LAIV)	7	0.22 [0.11–0.41]
Age 2–16 years (IIV)	5	0.36 [0.28–0.48]
Healthy adults	71	0.41 [0.36–0.47]
Age >65 years	30	0.42 [0.27–0.66]

Data compiled from Cochrane reviews on influenza vaccination preventing influenza in healthy adults, children and >65-year-olds [33–35]. LAIV: live attenuated influenza vaccine; IIV: inactivated influenza vaccine.

Causes of poor vaccine effectiveness

Longitudinal data spanning multiple influenza seasons has suggested poor vaccine-related immune responses in those undergoing repeated annual vaccination *versus* those who did not [41–43]. However, these findings remain controversial [44, 45]. One long-proposed theory for decreased vaccine effectiveness is “original antigenic sin” [46]. Original antigenic sin suggests that the first influenza viral antigens encountered in infancy (either through natural infection or vaccination) dictate an individual’s immune response throughout life. Antibodies induced by an individual’s first influenza vaccine are disproportionately upregulated by subsequent vaccines. This is because antigenic drift does not change the entire molecular structure of the HA or NA glycoprotein, so cross-reactivity to nondrifted regions remains. Therefore, historical plasma cells are upregulated in preference to production of an entirely new plasma cell subsets. This process is believed to cause narrower immune responses to vaccination, dependent upon tiny portions of the antigen. This means a significant mutation of these specific antigen portions could leave an individual with limited memory immune responses [47–49]. However, original antigenic sin can be both beneficial and detrimental in influenza immunity. During the 2009 pandemic, it was noted that older people had lower rates of infection *versus* the younger population, due to historical cross-immunity to conserved antigens from prior H1N1 viral infections (which were common in the late 1970s); thus their original antigenic exposure offered protection. A previously conserved antigen later mutated in the 2013–2014 H1N1 season, during which the older cohort was less protected and had a higher rate of influenza infection, while the younger generation who had immunity to other nondrifted antigens from the 2009 pandemic remained relatively protected [50–52]. This example highlights the pitfalls of vaccines unintentionally targeting narrow portions of specific epitopes. In addition, it highlights the issue with repeatedly vaccinating the most at-risk individuals, as counterintuitively, this may put them at greater risk. Further studies are needed to better categorise the effects of original antigenic sin and how this can be overcome by vaccination programmes.

Developing the universal vaccine

One method, currently of great interest to researchers, would be a universal vaccine. A universal vaccine induces broadly cross-reactive antibodies to a wide range of influenza virus strains and subtypes, which would remove the need for seasonal vaccine changes and administrations [48, 53, 54]. Furthermore, as the target antigens are conserved despite viral mutations, this would overcome concerns about original antigenic sin. Traditional influenza vaccines target the highly immunogenic, but modifiable, globular head of the HA glycoprotein spike. The most promising emerging strategy for the universal vaccine may be the targeting of the conserved stalk region of the HA glycoprotein [48, 53, 54]. The two major approaches to achieve a universal vaccine are firstly, to eliminate the immunodominant head region, and thus produce stalk-only viruses, and secondly, to use sequential vaccinations of conserved stalk regions but divergent HA head regions. Early-phase trials of universal vaccine candidates show promise in developing a desirable immune response [55]. However, studies are needed to assess safety, longevity of antibody response and clinical comparison against current vaccines. Additionally, the benefits of a universal vaccine may not overcome the deficit of immune responses in the elderly.

Ageing and vaccine effectiveness

It is well recognised that ageing has deleterious effects upon innate and adaptive immunity due to progressive “immunosenescence”. This process is both complex and has multiple influences upon the innate and adaptive immune system in the elderly. Immunosenescence includes (but is not limited to) the downregulation of phagocytosis and protein expression on dendritic cells and neutrophils; decreased production of naïve T- and B-lymphocytes; increased dysfunctional memory lymphocyte production; and involution of bone marrow and thymus activity [56]. Immunosenescence reduces vaccine efficacy, increases autoimmunity and impairs detection of neoplastic cells [57, 58]. Despite the increased importance of vaccinating the elderly due to their increased morbidity and mortality, the influenza vaccine has poor efficacy in this group, with a vaccine effectiveness of 17–53% *versus* 70–90% in young adults [59]. Furthermore, the period of vaccine protection appears to be <1 year [60]. One study demonstrated no increased protection against influenza infection *versus* nonvaccination after only 120 days [61]. Therefore, while the elderly are at highest risk of complications from influenza infection, our primary method of protection is less effective, and alternative strategies are required.

Strategies to overcome poor vaccine effectiveness in the elderly

One strategy for improving vaccine efficacy in the elderly is to increase the dose of HA antigen within the vaccine. This causes higher haemagglutinin inhibition titres and a more immunogenic vaccine [62]. One recent meta-analysis found that the higher-dose IIV increased effectiveness in preventing ILI, pneumonia, hospitalisation from influenza and a decreased influenza-related mortality *versus* standard-dose IIV, in those aged >65 years [63]. The higher-dose influenza vaccination reduced respiratory-related hospital

admissions in nursing home residents aged >65 years [64]. Other studies have found benefits mostly in those aged >85 years [65].

Intradermal vaccination is another possible method of improving vaccine efficacy, showing haemagglutinin inhibition levels either equivalent or superior to *i.m.* administration [66–68]. Interestingly, annual vaccination with intradermal administration in the elderly demonstrated improved immunogenicity, possibly overcoming the problems with original antigenic sin [66]. One proposed mechanism for the improved immunogenicity of intradermal vaccines is the increased number of antigen-presenting cells within the dermis. Furthermore, intradermal vaccination shows similar immune efficacy at a lower dose when compared to standard *i.m.* dose in the elderly [69], and this could potentially result in more cost-effective vaccine administration schedules.

The addition of adjuvants is another option for improving vaccine effectiveness. The development of new adjuvant trivalent inactivated vaccines (TIVa) has been shown to improve immune response when compared to nonadjuvant trivalent inactivated vaccines in the elderly, and reduced the risk of hospitalisation due to influenza and pneumonia by half [70, 71]. A meta-analysis of TIVa suggested a 94% reduction in ILI in the institutionalised elderly [71]. Other adjuvant strategies have been considered, including imiquimod (a Toll-like receptor 7 agonist) gel. A study found that when applied to the skin prior to the intradermal vaccine, participants had slower waning of antibody titres up to 1 year. In addition, participants had fewer hospitalisations for influenza or pneumonia [72]. Future high-quality research comparing high-dose and adjuvanted vaccination strategies in the elderly could be important to influence future public health strategy.

The indirect benefits to the vulnerable of vaccinating others

Given that the elderly mount less effective immune responses following vaccination, alternative strategies to protect this vulnerable group must be explored. One strategy already being utilised, approved by the WHO, is vaccination of healthcare workers. In contrast to the generally elderly “at-risk” population, most healthcare workers are young, healthy adults. They typically have higher seroconversion rates following vaccination and experience high vaccine effectiveness. These immunological advantages are thought to provide indirect protection for patients [73]. Indeed, vaccine uptake in healthcare workers has been found to be inversely associated with ILI in patients, and with reduced absence from work [74]. However, uptake remains low in many areas [75]. Possible reasons include lack of access to vaccination and lack of awareness of the benefits of vaccination [73]. While one study reported a 29% reduction in patient mortality, the net effects of vaccinating healthcare workers remains controversial, with some arguing that vaccination leads to no significant increased indirect protection and one meta-analysis reporting that the strength of the evidence is low [76–79]. Therefore, more robust studies are needed to assess the link between healthcare worker influenza vaccination and indirect protection for others.

Another possible method of protection is through the vaccination of children. Children are important vectors of influenza in the community due to high viral loads which increase infectiveness, an extended viral shedding period and their movement between schools and households [80–83]. Influenza B appears to have an increased attack rate among young children and infants, with those infected having an increased risk for emergency department attendances and intensive care admission [84–86]. In the UK it is recommended that school-aged children, and those aged 2–3 years old receive annual influenza vaccination, usually with the LAIV [87]. One statistical model suggested that vaccinating 50% of 2–18-year-olds could prevent 52 000 general practitioner (GP) consultations, 1500 cases of hospitalisation and 1200 deaths annually from influenza in England and Wales [88]. Ecological studies in Japan found lower rates of influenza, and a 36% adjusted mortality reduction in the over-65s due to influenza and pneumonia, when childhood influenza vaccine programmes were in place compared to when they were not [89]. There is evidence from randomised controlled and epidemiological studies where childhood influenza vaccination reduced population-level antibiotic prescriptions, GP visits, febrile illness and absenteeism from employment, influenza-related emergency department visits and intensive care unit admissions [90, 91]. Furthermore, the probability of an unvaccinated adult contracting influenza in the household is halved if any cohabiting children are vaccinated [92]. When compared with other childhood vaccines, influenza has been found to be highly cost-effective due to both direct and indirect benefits [93–95]. These data demonstrate that vaccinating children against influenza not only provides protection for the individual against disease, but may also provide indirect protection for the wider community. Encouraging vaccination of children may provide a vital tool for protecting the elderly and should be prioritised in public health strategy.

UK vaccination perspective

The UK’s Joint Committee on Vaccination and Immunisation (JCVI) recommends to the UK health departments the influenza vaccines that should be procured and administered to specific populations. The

TABLE 2 Summary of the influenza vaccine recommendations made in the joint Department of Health and Social Care, Public Health England and NHS England “annual flu letter”

	Vaccine
Age 2–17 years	Quadrivalent LAIV
Age 18–64 years (in clinical high-risk group due to illness, plus pregnant women, those in residential homes, carers, close contacts of immunocompromised)	Quadrivalent influenza vaccine: standard egg-grown or newly licensed cell-based vaccines
Age ≥65 years	Adjuvanted trivalent influenza vaccine or cell-based quadrivalent influenza vaccine. High-dose trivalent vaccine is licensed, but not currently funded under the NHS as it has a significantly higher price

LAIV: live attenuated influenza vaccine; NHS: National Health Service.

JCVI's recommendation from late 2017 was that all people aged ≥ 65 years should be offered the adjuvanted inactivated trivalent vaccine. This advice has since been further updated so that quadrivalent cell-cultured inactivated vaccine and high-dose trivalent vaccine are equally suitable, in this group [96].

Based on JCVI advice, the Department of Health and Social Care, Public Health England and NHS England have issued their annual joint influenza immunisation programme plan for the 2019–2020 influenza season (summarised in table 2) [15]. The target uptake proportion in the ≥ 65 years group is 75%, in line with the WHO target for this group. GPs and school providers are tasked with actively inviting 100% of eligible individuals for their vaccine.

Comparing the UK perspective with approaches in European Union countries

The UK has the highest uptake of influenza vaccination compared to its European counterparts, as well as being the only nation to use different administration routes depending upon age group [97, 98]. There are a wide variety of approaches throughout both member and nonmember states of the European Union (EU) regarding influenza vaccination schedules. Of concern, the mean percentage vaccination rate of the elderly for 19 member states was 47.1% (ranging from 2% to 72.8%) in the influenza 2016–2017 session [97]. This is below the EU's target for at-risk groups of 75%, with average whole-population vaccination rate declining across Europe as a whole [97, 98]. Only 17 out of 31 nations across Europe recommended vaccinating infants or children. 29 out of the 30 member states endorsed healthcare worker immunisation, and 28 suggested vaccinating pregnant women (although suggestions on the optimal timing vary). All member states suggested protecting those with a history of pulmonary, cardiovascular, renal or metabolic comorbidities [97, 98].

Conclusions and future research

In conclusion, vaccination is currently advised for vulnerable groups, including children and elderly people. Immunosenescence may reduce vaccine efficacy and effectiveness in the elderly, with alternative delivery systems, higher doses and vaccine adjuvants being developed to overcome this. There is strong evidence that indirect protection for the community can be gained by vaccinating children and healthcare workers. This should be utilised to protect older people, but must be balanced against the potential risks of original antigenic sin. Prospective adequately powered studies are required to definitively answer whether indirect protection can be conferred to the elderly, and if proven this can be utilised to prevent disease in this immunologically vulnerable population. Further research into the development of the universal vaccine is needed to assess its effectiveness against multiple strains of influenza, but it provides promising avenues for future research.

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