Influenza Vaccination: Protecting the Most Vulnerable

Alex R Tanner1\*, Robert B Dorey2, Nathan J Brendish3,4, Tristan W Clark3,4,5,6

1. Department of Medicine for the Elderly, The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, Dorset, UK

2. NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3. School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

4. Department of Infection, University Hospital Southampton NHS Foundation Trust, Southampton, UK

5. NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

6. NIHR Post Doctoral Fellowship Programme, UK

\* Corresponding author: Dr Alex Robert Tanner, Department of Medicine for the Elderly, Royal Bournemouth Hospital, Castle Lane East, BH7 7DW, Post point F25, Education Centre, OPM/Stroke Office

alextanner757@gmail.com, Telephone Number: 0044(0)1202726175, Fax Number: 01202704303

**Keywords**: influenza, vaccine, adjuvant, elderly, immunosenescence, original antigen sin, universal vaccine

# Take Home message

To protect the elderly from influenza multiple strategies to overcome immunosenescence need to be utilised, such as: improving vaccine efficacy, in-direct protection via vaccinating children and healthcare workers and developing a universal vaccine.

# Highlights

* Influenza vaccination is updated annually due to mutations in circulating viruses
* Influenza burden disproportionately affects the elderly
* Vaccine effectiveness in the elderly is low due to immunosenescence
* Immunogenicity can be improved in the elderly by high-dose or adjuvanted vaccines
* Universal vaccines against conserved regions of the virus are in development

# 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 over 65 years receive an adjuvanted trivalent inactivated vaccine, and adults under 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 underway.

# 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, approximately 100,000 deaths occur in children under five years old, and 120,000 to 240,000 deaths occur in people over 75 years old(1,4). Other populations at risk of severe morbidity and mortality are: 1) pregnant women (particularly during the third trimester) 2) immunocompromised individuals 3) those with multiple co-morbidities(5–11); the latter two risk factors are more common in older people. Seasonal influenza is estimated to reduce annual gross domestic product (GDP) in the UK by 0.5-4.3% (£8.4-72.3 billion)(12). In the US, the estimated annual direct medical costs of seasonal influenza were $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 SARS-CoV2 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-CoV2 with seasonal influenza. Although reports from Hong Kong showed a shortened influenza session with fewer cases, likely 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-naive(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 the replication, there is a high frequency of point mutations to the HA gene. HA in 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 Organisation (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 around 25% in England 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 non-vaccination(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 and a 37% reduction in those over 65 years old. 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 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).

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 an NNT of only 7 and 20, respectively. IIV reduced risk of influenza from 30% to 11% and ILI from 28% to 20%, in children (NNT: 5 and 12 for influenza and ILI, respectively)(34). In the over 65s, the vaccine reduced the risk of influenza from 6% to 2.4% (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.

|  |  |  |  |
| --- | --- | --- | --- |
| Groups | NNT against Influenza | Relative Risk | Confidence Intervals |
| Age 3-16 (LAIV)  | 7 | 0.22 | 0.11-0.41 |
| Age 2-16 (IIV) | 5 | 0.36 | 0.28-0.48 |
| Healthy Adults | 71 | 0.41 | 0.36-0.47 |
| Over 65’s | 30 | 0.42 | 0.27-0.66 |

Table 1: Summary of the number needed to treat with the influenza vaccine vs different age groups to protect against influenza.

Data compiled from Cochrane reviews on influenza vaccination preventing influenza in healthy adults, children and over 65-year olds(33–35).

# 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 greater than 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 laboratory-confirmed influenza (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.

# Causes for poor vaccine effectiveness

Longitudinal data spanning multiple influenza seasons has suggested poor vaccine-related immune responses in those undergoing repeated annual vaccination versus with 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 non-drifted regions remains. Therefore, historical plasma cells are up‑regulated 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 non-drifted antigens from the 2009 pandemic remained relatively protected(50–52). This example highlights the pitfalls of vaccines unintentionally targeting narrow portions of specific epitopes. It also 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 over-come 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 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 immuno-dominant head region, thus produce stalk only viruses, and secondly, use sequential vaccinations 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 antibodies response and clinical comparison against current vaccines. Additionally, the benefits of a universal vaccine may not overcome the deficit of immune responses 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. Including (but not limited too): 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 less than one year(60). One study demonstrated no increased protection against influenza infection versus non-vaccination 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 is 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 the over 65s(63). With the higher dose influenza vaccination reducing respiratory related hospital admissions in over 65-years-old nursing home residents(64). Other studies have found benefits mostly in the over 85s(65).

Intradermal vaccination is another possible method of improving vaccine efficacy, showing haemagglutinin inhibition levels either equivalent or superior to IM 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 IM 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 non-adjuvant 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 imiqimod (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 one year. Participants also 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, which is approved by the WHO, is vaccination of healthcare workers (HCW). In contrast to the, generally elderly, ‘at risk’ population, most HCW 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 HCWs 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 HCWs 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 HCW 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 to 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 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 co-habiting 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). This data demonstrates 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 JCVI’s recommendation from late 2017 was that all people aged 65 or older 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 & 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 and over 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.

Table 2: Summary of the influenza vaccine recommendations made in the joint Department of Health & Social Care, Public Health England, and NHS England “Annual Flu Letter”

|  |  |
| --- | --- |
| **Age Group** | **Vaccine**  |
| 2 to 17 years | Quadravalent Live Attenuated Influenza Vaccine (LAIV) |
| 18 to 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 (QIV): standard egg-grown (QIVe) or newly licenced cell-based vaccines (QIVc) |
| 65 years and over | Adjuvanted trivalent influenza vaccine (aTIV) or QIVc. High dose trivalent vaccine (TID-HD) is licenced but not currently funded under the NHS as it has a significantly higher price |

# Comparing the UK perspective with other EU countries approaches

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 non-member states of the European Union (EU) regarding influenza vaccination schedules. Of concern, the mean percentage vaccination rate for 19 member states of the elderly was 47.1% (ranging from 2-72.8%) 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 HCW immunisation, 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 co-morbidities(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 provides promising avenues for future research.

# Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

# Declarations of interest

ART, RBD, and NJB have no conflicts of interest to declare. TWC has received speaker fees, honoraria, travel reimbursement, and equipment and consumables free of charge for the purposes of research outside of this submitted study, from BioFire diagnostics LLC and BioMerieux. TWC has received consultancy fees from Synairgen research Ltd, Randox laboratories Ltd and Cidara therapeutics. He has been a member of advisory boards for Roche and a member of two independent data monitoring committees for trials sponsored by Roche. He has acted as the UK chief investigator for a study sponsored by Janssen.

This report is independent research supported by the National Institute for Health Research (NIHR Post Doctorial Fellowship, Dr Tristan Clark, PDF 2016-09-061). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. NJB is supported by a NIHR Clinical Lecturer post.

# References

1. World Health Organisation. Influenza (Seasonal) - Fact Sheet. 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). [Last accessed 22nd July 2020].

2. Ghebrehewet S, MacPherson P, Ho A. Influenza. BMJ. 2016 Dec 7;i6258.

3. Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, Doherty PC, et al. Influenza. Nat Rev Dis Prim. 2018;4(1):3.

4. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018 Mar;391(10127):1285–300.

5. World Health Organisation. Vaccine against influenza WHO position paper - November 2012. Weekly Epidemiological Record. 2012;47(87):461–76.

6. Meijer WJ, Van Noortwijk AGA, Bruinse HW, Wensing AMJ. Influenza virus infection in pregnancy: A review. Acta Obstet Gynecol Scand. 2015;94(8):797–819.

7. Memoli MJ, Athota R, Reed S, Czajkowski L, Bristol T, Proudfoot K, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. Clin Infect Dis. 2014;58(2):214–24.

8. Greenbaum A, Chaves SS, Perez A, Aragon D, Bandyopadhyay A, Bennett N, et al. Heavy alcohol use as a risk factor for severe outcomes among adults hospitalized with laboratory-confirmed influenza, 2005–2012. Infection. 2014 Feb 16;42(1):165–70.

9. Vogel P, Rosch J, Tuomanen E, Schultz-Cherry S, Meliopoulos VA, van de Velde L-A, et al. A Perfect Storm: Increased Colonization and Failure of Vaccination Leads to Severe Secondary Bacterial Infection in Influenza Virus-Infected Obese Mice. MBio. 2017;8(5):1–15.

10. van Kerkhove MD, Vandemaele KAH, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza a (H1N1) infection: A global pooled analysis. PLoS Med. 2011;8(7).

11. Walker JL, Zhao H, Dabrera G, Andrews N, Thomas SL, Tsang C, et al. Assessment of Effectiveness of Seasonal Influenza Vaccination During Pregnancy in Preventing Influenza Infection in Infants in England, 2013-2014 and 2014-2015. J Infect Dis. 2019;221.

12. Smith RD, Keogh-Brown MR, Barnett T, Tait J. The economy-wide impact of pandemic influenza on the UK: a computable general equilibrium modelling experiment. BMJ. 2009 Nov 19;339(nov19 1):b4571–b4571.

13. Putri WCWS, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. Vaccine. 2018;36(27):3960–6.

14. Public Health England. The national influenza immunisation programme 2019 to 2020: Inactivated influenza vaccine information for healthcare practitioners. 2019. Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attach

ment\_data/file/847840/Inactivated\_influenza\_vaccine\_information\_for\_healthcare\_

practitioners\_2019-20\_Nov.pdf. [Last accessed July 23rd 2020]

15. Public Health England. Annual National Flu programme letter 2019 to 2020. 2019. Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attach

ment\_data/file/788903/Annual\_national\_flu\_programme\_2019\_to\_2020\_.pdf. [Last

accessed 23rd July 2020]

16. New South Wales Government. Seasonal influenza vaccination 2020. Available from:

https://www.health.nsw.gov.au/immunisation/Pages/flu.aspx. [Last accessed 22nd

July 2020]

17. Chan KH, Lee P, Chan CY, Lam KBH, Ho P. Monitoring respiratory infections in covid-19 epidemics. BMJ. 2020 May 4;m1628.

18. Paules C, Subbarao K. Influenza. Lancet. 2017;390(10095):697–708.

19. Uyeki TM, Peiris M. Novel Avian Influenza A Virus Infections of Humans. Infect Dis Clin North Am. 2019;33(4):907–32.

20. Tong S, Zhu X, Li Y, Shi M, Zhang J, Bourgeois M, et al. New World Bats Harbor Diverse Influenza A Viruses. PLoS Pathog. 2013;9(10).

21. Munster VJ, Wallensten A, Waldenstrom J, Fouchier RAM, Osterhaus ADME, Olsen B. Global Patterns of Influenza A Virus in Wild Birds. Science (80- ). 2006;312(5772):384–8.

22. Lopez I, Faix D, St. George K, Stringer DJ, Lindstrom S, Smole S, et al. Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans. Science (80- ). 2009;325(5937):197–201.

23. Rondy M, Kissling E, Emborg H-D, Gherasim A, Pebody R, Trebbien R, et al. Interim 2017/18 influenza seasonal vaccine effectiveness: combined results from five European studies. Eurosurveillance. 2018 Mar 1;23(9):1–12.

24. Lee BY, Bartsch SM, Willig AM. The economic value of a quadrivalent versus trivalent influenza vaccine. Vaccine. 2012 Dec;30(52):7443–6.

25. Dbaibo G, Amanullah A, Claeys C, Izu A, Jain VK, Kosalaraksa P, et al. Quadrivalent Influenza Vaccine Prevents Illness and Reduces Healthcare Utilization Across Diverse Geographic Regions During Five Influenza Seasons. Pediatr Infect Dis J. 2019;39(1):1.

26. Thorrington D, van Leeuwen E, Ramsay M, Pebody R, Baguelin M. Cost-effectiveness analysis of quadrivalent seasonal influenza vaccines in England. BMC Med. 2017;15(1):1–9.

27. Van Bellinghen LA, Meier G, Van Vlaenderen I. The potential cost-effectiveness of quadrivalent versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: A lifetime multi-cohort model. PLoS One. 2014;9(6).

28. de Boer PT, Kelso JK, Halder N, Nguyen T-P-L, Moyes J, Cohen C, et al. The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia. Vaccine. 2018;36(7):997–1007.

29. Hoft DF, Lottenbach KR, Blazevic A, Turan A, Blevins TP, Pacatte TP et al. Comparisons of the humoral and cellular immune responses induced by live attenuated influenza vaccine and inactivated influenza vaccine in adults. Clin Vaccine Immunol. 2017;24(1):e00414.

30. Ashkenazi S, Vertruyen A, Aristegui J, Esposito S, McKeith DD, Klemola T, et al. Superior Relative Efficacy of Live Attenuated Influenza Vaccine Compared With Inactivated Influenza Vaccine in Young Children With Recurrent Respiratory Tract Infections. Pediatr Infect Dis J. 2006 Oct;25(10):870–9.

31. Kemble G, Black S V, Connor EM, Vesikari T, Hultquist M, Edwards KM, et al. Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children. N Engl J Med. 2007;356(7):685–96.

32. Rondy M, El Omeiri N, Thompson MG, Levêque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. J Infect. 2017 Nov;75(5):381–94.

33. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2018 Feb 1.

34. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev. 2018 Feb 1.

35. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018 Feb 1.

36. Verschoor CP, Singh P, Russell ML, Bowdish DME, Brewer A, Cyr L, et al. Microneutralization assay titres correlate with protection against seasonal influenza H1N1 and H3N2 in children. PLoS One. 2015;10(6):7–13.

37. Paccalin M, Plouzeau C, Bouche G, Guillard O, Beby-Defaux A, Mauco G, et al. Lack of correlation between nutritional status and seroprotection against influenza in a long term care facility. Scand J Infect Dis. 2006 Jan 8;38(10):894–7.

38. Lewnard J, Cobey S. Immune History and Influenza Vaccine Effectiveness. Vaccines. 2018;6(2):28.

39. Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza vaccine effectiveness. Vaccine. 2017;35(36):4796–800.

40. Shi M, An Q, Ainslie KEC, Haber M, Orenstein WA. A comparison of the test-negative and the traditional case-control study designs for estimation of influenza vaccine effectiveness under nonrandom vaccination. BMC Infect Dis. 2017;17(1):757.

41. Saito N, Komori K, Suzuki M, Morimoto K, Kishikawa T, Yasaka T, et al. Negative impact of prior influenza vaccination on current influenza vaccination among people infected and not infected in prior season: A test-negative case-control study in Japan. Vaccine. 2017;35(4):687–93.

42. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis. 2014 Nov 15;59(10):1375–85.

43. Saito N, Komori K, Suzuki M, Kishikawa T, Yasaka T, Ariyoshi K. Dose-Dependent Negative Effects of Prior Multiple Vaccinations Against Influenza A and Influenza B Among Schoolchildren: A Study of Kamigoto Island in Japan During the 2011–2012, 2012–2013, and 2013–2014 Influenza Seasons. Clin Infect Dis. 2018 Aug 31;67(6):897–904.

44. Beyer WEP, de Bruijn IA, Palache AM, Westendorp RGJ, Osterhaus ADME. Protection Against Influenza After Annually Repeated Vaccination. Arch Intern Med. 1999 Jan 25;159(2):182.

45. McLean HQ, Caspard H, Griffin MR, Gaglani M, Peters TR, Poehling KA, et al. Association of Prior Vaccination With Influenza Vaccine Effectiveness in Children Receiving Live Attenuated or Inactivated Vaccine. JAMA Netw Open. 2018 Oct 26;1(6):e183742.

46. Francis TJ. On the Doctrine of Original Antigenic Sin. Proc Am Philos Soc. 1960;104(6):572–8.

47. Kim JH, Skountzou I, Compans R, Jacob J. Original Antigenic Sin Responses to Influenza Viruses. J Immunol. 2009 Sep 1;183(5):3294–301.

48. Henry C, Palm A-KE, Krammer F, Wilson PC. From Original Antigenic Sin to the Universal Influenza Virus Vaccine. Trends Immunol. 2018;39(1):70–9.

49. Sanyal M, Holmes TH, Maecker H, Albrecht RA, Dekker CL, He X-S, et al. Diminished B-Cell Response After Repeat Influenza Vaccination. J Infect Dis. 2018 Nov 28.

50. Cobey S, Hensley SE. Immune history and influenza virus susceptibility. Curr Opin Virol. 2017 Feb;22:105–11.

51. Wilson PC, Esposito S, Hensley SE, Linderman SL, Madara J, Wrammert J, et al. Immune history shapes specificity of pandemic H1N1 influenza antibody responses. J Exp Med. 2013;210(8):1493–500.

52. Dávila-Torres J, Chowell G, Borja-Aburto VH, Viboud C, Grajalez-Muñiz C, Miller MA. Intense Seasonal A/H1N1 Influenza in Mexico, Winter 2013–2014. Arch Med Res. 2015 Jan;46(1):63–70.

53. Krammer F. The human antibody response to influenza A virus infection and vaccination. Nat Rev Immunol. 2019;19(6):383–97.

54. Krammer F. Novel universal influenza virus vaccine approaches. Curr Opin Virol. 2016;17:95–103.

55. Bernstein DI, Guptill J, Naficy A, Nachbagauer R, Berlanda-Scorza F, Feser J, et al. Immunogenicity of chimeric haemagglutinin-based, universal influenza virus vaccine candidates: interim results of a randomised, placebo-controlled, phase 1 clinical trial. Lancet Infect Dis. 2019;3099(19):1–12.

56. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol. 2018 Dec;40:83–94.

57. Haq K, McElhaney JE. Immunosenescence: influenza vaccination and the elderly. Curr Opin Immunol. 2014 Aug;29:38–42.

58. Haralambieva IH, Painter SD, Kennedy RB, Ovsyannikova IG, Lambert ND, Goergen KM, et al. The Impact of Immunosenescence on Humoral Immune Response Variation after Influenza A/H1N1 Vaccination in Older Subjects. Stambas J, editor. PLoS One. 2015 Mar 27;10(3):e0122282.

59. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: A quantitative review. Vaccine. 2006 Feb 20;24(8):1159–69.

60. Wilder-Smith A, Parry CM, Cook AR, I-Cheng MC, Young B, Zhao X. Do antibody responses to the influenza vaccine persist year-round in the elderly? A systematic review and meta-analysis. Vaccine. 2016;35(2):212–21.

61. Castilla J, Martínez-Baz I, Martínez-Artola V, Reina G, Pozo F, García Cenoz M, et al. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. Eurosurveillance. 2013 Jan 31;18(5):1–8.

62. DiazGranados CA, Kirby D, Pollak R, Collins A, Decker MD, Kimmel M, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. N Engl J Med. 2014;371(7):635–45.

63. Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines. 2018 May 4;17(5):435–43.

64. Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017;5(9):738–46.

65. Richardson DM, Medvedeva EL, Roberts CB, Linkin DR. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccination in Community-Dwelling Veterans. Clin Infect Dis. 2015;61(2):171–6.

66. Arnou R, Icardi G, De Decker M, Ambrozaitis A, Kazek M-P, Weber F, et al. Intradermal influenza vaccine for older adults: A randomized controlled multicenter phase III study. Vaccine. 2009 Dec;27(52):7304–12.

67. Young F, Marra F. A systematic review of intradermal influenza vaccines. Vaccine. 2011 Nov;29(48):8788–801.

68. Holland D, Booy R, Looze F De, Eizenberg P, McDonald J, Karrasch J, et al. Intradermal Influenza Vaccine Administered Using a New Microinjection System Produces Superior Immunogenicity in Elderly Adults: A Randomized Controlled Trial. J Infect Dis. 2008 Sep;198(5):650–8.

69. Chi R, Rock MT, Neuzil KM. Immunogenicity and Safety of Intradermal Influenza Vaccination in Healthy Older Adults. Clin Infect Dis. 2010 May 15;50(10):1331–8.

70. Tsai TF. Fluad®-mf59®-adjuvanted influenza vaccine in older adults. Infect Chemother. 2013;45(2):159–74.

71. Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. Vaccine. 2017;35(4):513–20.

72. Hung IFN, Zhang AJ, To KKW, Chan JFW, Li C, Zhu H-S, et al. Immunogenicity of Intradermal Trivalent Influenza Vaccine With Topical Imiquimod: A Double Blind Randomized Controlled Trial. Clin Infect Dis. 2014 Nov 1;59(9):1246–55.

73. Kliner M, Keenan A, Sinclair D, Ghebrehewet S, Garner P. Influenza vaccination for healthcare workers in the UK: Appraisal of systematic reviews and policy options. BMJ Open. 2016;6(9).

74. Pereira M, Williams S, Restrick L, Cullinan P, Hopkinson NS. Healthcare worker influenza vaccination and sickness absence – an ecological study. Clin Med. 2017;17(6):484–93.

75. Amodio E, Restivo V, Firenze A, Mammina C, Tramuto F, Vitale F. Can influenza vaccination coverage among healthcare workers influence the risk of nosocomial influenza-like illness in hospitalized patients? J Hosp Infect. 2014 Mar;86(3):182–7.

76. Dini G, Toletone A, Sticchi L, Orsi A, Bragazzi NL, Durando P. Influenza vaccination in healthcare workers: A comprehensive critical appraisal of the literature. Hum Vaccines Immunother. 2018;14(3):772–89.

77. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. Cochrane Database Syst Rev. 2016 Jun 2.

78. Ahmed F, Lindley MC, Allred N, Weinbaum CM, Grohskopf L. Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: Systematic review and grading of evidence. Clin Infect Dis. 2014;58(1):50–7.

79. Ward BJ, Loeb M, Lemieux C, Collignon P, Gardam M, Patrick DM, et al. Influenza Vaccination of Healthcare Workers: Critical Analysis of the Evidence for Patient Benefit Underpinning Policies of Enforcement. PLoS One. 2017;12(1):e0163586.

80. Principi N. Burden of influenza in healthy children and their households. Arch Dis Child. 2004;89(11):1002–7.

81. Cauchemez S, Valleron A-J, Boëlle P-Y, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from Sentinel data. Nature. 2008 Apr 10;452:750.

82. Cauchemez S, Ferguson NM, Fox A, Mai LQ, Thanh LT, Thai PQ, et al. Determinants of Influenza Transmission in South East Asia: Insights from a Household Cohort Study in Vietnam. PLoS Pathog. 2014;10(8):2–9.

83. Viboud C, Boëlle PY, Cauchemez S, Lavenu A, Valleron AJ, Flahault A, et al. Risk factors of influenza transmission in households. Br J Gen Pract. 2004;54(506):684–9.

84. Caini S, Spreeuwenberg P, Kusznierz GF, Rudi JM, Owen R, Pennington K, et al. Distribution of influenza virus types by age using case-based global surveillance data from twenty-nine countries, 1999-2014. BMC Infect Dis. 2018;18(1).

85. Olson DR, Heffernan RT, Paladini M, Konty K, Weiss D, Mostashari F. Monitoring the impact of influenza by age: Emergency department fever and respiratory complaint surveillance in New York City. PLoS Med. 2007;4(8):1349–61.

86. Tran D, Vaudry W, Moore D, Bettinger JA, Halperin SA, Scheifele DW, et al. Hospitalization for influenza A versus B. Pediatrics. 2016;138(3).

87. Public Health England. The routine immunisation schedule. 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/824542/PHE\_complete\_immunisation\_schedule\_autumn\_2019.pdf [last accessed 22nd July 2020].

88. Pitman RJ, White LJ, Sculpher M. Estimating the clinical impact of introducing paediatric influenza vaccination in England and Wales. Vaccine. 2012;30(6):1208–24.

89. Simonsen L, Sturm-Ramirez K, Sugaya N, Chowell G, Shinjoh M, Charu V, et al. Influenza-Related Mortality Trends in Japanese and American Seniors: Evidence for the Indirect Mortality Benefits of Vaccinating Schoolchildren. PLoS One. 2011;6(11):e26282.

90. Hurwitz ES. Effectiveness of Influenza Vaccination of Day Care Children in Reducing Influenza-Related Morbidity Among Household Contacts. JAMA. 2000 Oct 4;284(13):1677.

91. Elliot AJ, Boddington NL, Mullett D, Green HK, Donati M, Smith GE, et al. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. Eurosurveillance. 2015;20(39):1–11.

92. Perera RAPM, Tsang TK, Cowling BJ, Peiris JSM, So HC, Fang VJ, et al. Indirect protection from vaccinating children against influenza in households. Nat Commun. 2019;10(1):25–8.

93. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: A cost-effectiveness study. BMC Med. 2015;13(1):1–13.

94. Gibson E, Begum N, Sigmundsson B, Sackeyfio A, Hackett J, Rajaram S. Economic evaluation of pediatric influenza immunization program compared with other pediatric immunization programs: A systematic review. Hum Vaccines Immunother. 2016;12(5):1202–16.

95. Ting EEK, Sander B, Ungar WJ. Systematic review of the cost-effectiveness of influenza immunization programs. Vaccine. 2017 Apr;35(15):1828–43.

96. JCVI. JOINT COMMITTEE ON VACCINATION AND IMMUNISATION. In: Minute of the meeting on 04 October 2017. 2017. p. 1–16. Available from: http://app.box.com/s/iddfb4ppwkmtjusir2tc/file/247634612957. [Last accessed 22nd July 2020].

97. Mereckiene J. European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States – Overview of vaccine recommendations for 2017–2018 and vaccination coverage rates for 2015–2016 and 2016–2017 influenza seasons. ECDC. 2018. Available from: https://ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-antiviral-use-eu-eea-member-states. [Last accessed 22nd September 2020]

98. ECDC. Influenza: Recommended vaccinations. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=15&SelectedCountryIdByDisease=-1. [Last accessed 22nd September 2020].