Review of evidence to inform the New Zealand National Immunisation Programme, 2025: Influenza – enhanced vaccines

Prepared by Dr Mary Nowlan, on behalf of the Immunisation Advisory Centre

Review conducted as part of a contract for services for the National Immunisation Programme at Health New Zealand | Te Whatu Ora

September 2025 (edited October 2025)

Immunisation Advisory Centre

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Abbreviations

AE	adverse events
AEFI	adverse events following immunisation
AESI	adverse events of special interest
aIIV / aTIV / aQIV	adjuvanted inactivated influenza vaccine / trivalent / quadrivalent
ARI	acute respiratory tract infection
ATAGI	Australian Technical Advisory Group on Immunisation
ATSI	Aboriginal and Torres Strait Island peoples
aVE	adjusted vaccine efficacy / effectiveness
CDC	Centers for Disease Control and Prevention
CLL	chronic lymphocytic leukaemia
95% CI	95% confidence interval
ELISA	enzyme-linked immunosorbent assay
EMR	electronic medical records
ESR / PHF Science	Institute of Environmental Surveillance and Research, now New Zealand Institute of Public Health and Forensic Science
EU	European Union
FDA	Food and Drug Administration (US)
FRNT	focal reduction neutralisation tests
GB	Great Britain
GBS	Guillain-Barré syndrome
GI	gastrointestinal
GMT	geometric mean titre
GMTR	geometric mean titre ratio
HA	haemagglutinin
HAI	haemagglutinin inhibition assay
HAART	highly active anti-retroviral therapy
hd-IIV / hd-TIV / hd-QIV	high dose inactivated influenza vaccine / trivalent / quadrivalent
HIV	human immunodeficiency virus
HR	hazard ratio
HSCT	haematopoietic stem cell transplantation
IBD	inflammatory bowel disease
ICU	intensive care unit
IFN-γ	interferon gamma
IIV / IIVc / IIVe	inactivated influenza vaccine – cell-based, egg-based
ILI	influenza-like illness
IPTW	inverse probability of treatment weighting
IRME	influenza-related medical encounter
IRR	incidence rate ratio
JVCI	Joint Committee for Vaccination and Immunisation (UK)
KPNC / KPSC	Kaiser Permanente Northern California / Southern California
LAIV	live attenuated influenza vaccine
LRT / LRTI	lower respiratory tract / infection
mAb	monoclonal antibody
MBL	monoclonal B cell lymphocytosis
MDCK	Madin-Darby canine kidney cells
MenACWY	quadrivalent meningococcal vaccine
MFR	mean fold rise
MI	myocardial infarction
MN	micro-neutralisation assay
NA	neuraminidase
NACI	National Advisory Committee on Immunization (Canada)
NZ	Aotearoa New Zealand
QIVc	cell-based quadrivalent influenza vaccine
QIVe / TIVe	egg-based quadrivalent / trivalent influenza vaccine
RCT	randomised controlled trial
RIV / RIV3 / RIV 4	recombinant influenza vaccine / trivalent / quadrivalent
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
rVE	relative vaccine effectiveness
rZV	recombinant zoster vaccine
SAE	serious adverse event
SARI	severe acute respiratory tract infection
SD	standard dose
SR, SR/MA	systematic review, systematic review / meta-analysis
TIV, TIVc	trivalent influenza vaccine, cell-based
URT / URTI	upper respiratory tract / infection
US	United States of America
UK	United Kingdom
VE	vaccine efficacy / effectiveness
vs	versus
WHO	World Health Organization

Executive Summary

This review of evidence examines the benefits of 'enhanced' seasonal influenza vaccines, including high-dose, adjuvanted, cell-based and recombinant subunit formulations over standard-dose inactivated influenza vaccines in adults. It will also briefly review recent evidence around the use of live attenuated influenza vaccine, particularly in children.

As it follows previous reviews on influenza, only recently published evidence has been reviewed, primarily between January 2019 to June 2025. The goal is to inform the influenza immunisation programme in Aotearoa New Zealand (NZ) and the Immunisation Handbook about the potential of these enhanced vaccines, including those not yet approved for use in New Zealand. This is not a systematic review, the quality of the evidence has not been formally graded, and it does not consider cost-benefit analysis. The opinions and interpretations of the literature presented are solely those of the author.

Burden of influenza

The highest incidence of severe influenza is predominantly in children aged under 4 years and in adults aged over 65 years. Standard inactivated influenza vaccine is funded for those aged over 65 years but is only funded for children aged from 6 months to under 5 years who have previously been hospitalised with a respiratory illness or those with an underlying health condition that is eligible for funded vaccine. No 'enhanced' influenza vaccine is currently funded for any group.

Advancements in influenza vaccine technology

Standard inactivated influenza vaccines (IIV) offer modest and variable protection against symptomatic influenza, at around 50% effectiveness, particularly for those at the highest risk of severe influenza complications and death. Seasonal influenza vaccination serves to lessen the burden of seasonal respiratory infections on both the health system and individuals; to slow transmission of influenza within the population; and to reduce sequalae influenza infection, such as cardiovascular events, secondary invasive bacterial infections, and loss of independence and increasing frailty in older adults.

A significant challenge for the current seasonal influenza vaccines is matching the vaccine virus with the circulating strains. Mismatch can result either from changes in the wild-type virus or in the vaccine virus during manufacture, which can severely limit vaccine effectiveness during some seasons. Conventional IIV are propagated in hens' eggs (IIVe), which can lead to a manufacturing mismatch due to 'egg-adaptation' mutations.

The virus strains used in IIV are chemically inactivated and disrupted (as used in split-virion vaccines). They can be further refined to produce subunit vaccines by isolating the major surface antigens, haemagglutinin (HA) and neuraminidase (NA). These vaccines are administered intramuscularly to elicit a surface antigen-specific, systemic immune response.

- *Cell-based propagation*: To address egg-adaptation during manufacture, cell-based influenza vaccine uses virus propagated in mammalian cells instead of eggs (IIVc, trivalent TIVc or

quadrivalent QIVc. By using cell-lines, this vaccine can be produced in large volumes more rapidly than in eggs. Brand name: Flucelvax® (CSL Seqirus)

- *Adjuvant*: Immunogenicity of IIV can be enhanced using various strategies. A squalene-oil-water emulsion adjuvant (MF59®) is added to standard IIV to produce adjuvanted IIV (aIIV, aTIV or aQIV). Currently, produced in eggs but a cell-based formulation is in late-stage clinical development (aTIVc) Brand name: Fluad ® and Fluad® Quad (CSL Seqirus)
- *High dose*: Another approach to induce a stronger immune response is to use a higher dose of haemagglutinin (60µg vs 15µg per strain in standard IIV) (hd-IIV, trivalent hd-TIV, quadrivalent hd-QIV). Brand name: Fluzone® High-Dose (Sanofi)

Instead of propagating whole influenza virus to isolate haemagglutinin, recombinant, strain-matched, pure haemagglutinin is produced using a baculovirus vector system in insect cells. This means that large quantities of haemagglutinin, genetically matched to predominant strains, can be produced more rapidly than for inactivated influenza vaccines. Recombinant haemagglutinin is less glycosylated than haemagglutinin produced through viral propagation, and as such, is predicted to have more epitopes available to the immune system to improve the breadth of the immune response.

- *Recombinant influenza vaccine* (RIV, trivalent RIV3 or quadrivalent RIV4) contains a high dose (45µg) of purified strain-matched haemagglutinin. Brand name: FluBlok® or Supemteck® (Sanofi)

As an alternative to a systemic response against the haemagglutinin and neuraminidase only, as for IIV, a targeted immune response within the nasal mucosa can be achieved directly by administering live attenuated virus intranasally, mimicking the wild-type viral infection.

- *Live attenuated influenza vaccine (LAIV):* LAIV has successfully be used in children. Brand name: FluMist® or Fluenz® (AstraZeneca).

Comparison of safety

The safety of 'enhanced' inactivated influenza vaccines is in line with those of other non-live vaccines, including standard influenza vaccine (see Table 1). Some increase in reactogenicity, particularly mild to moderate injection site reactions, is seen in the adjuvanted, high-dose and recombinant vaccines, but this is reported mostly in younger age groups who have generally have a robust immune response to vaccines. The benefit of using higher doses or adjuvants is to improve responses in older people and in those less likely to respond well to standard vaccines, and therefore the reactogenicity is not noticeably increased in these groups.

It is important to consider safety of these vaccines when used in combination with other vaccines. Increasingly, a range of vaccines are being used in older adults and immunocompromised groups, some of which contain proprietary adjuvants. These include RSV, zoster, pneumococcal and COVID-19 vaccines. Coadministration was associated with slightly higher reactogenicity but was generally in line with the reactogenicity of the vaccines when given separately.

The potential responses to LAIV include the upper respiratory tract infection-type symptoms, such as nasal congestion, sore throat and rhinorrhoea. Caution remains around the use of this vaccine in young children with a history of wheeze but appears not to be a safety concern in those aged over 2

years and risk is outweighed by the benefit in protection against influenza in children with asthma. Although contraindicated for those with severe immunocompromise, evidence shows safety in children living with well-controlled HIV infection.

Table 1: Comparison of safety of enhanced influenza vaccines.

Vaccine Type	Summary
Cell-based	Excellent safety across all age groups. Mild local reactions only. Comparable to egg-based vaccines.
Adjuvanted	Slightly more reactogenic than standard IIV. Well-established safety. Good safety in frail and immunocompromised individuals.
High dose	More frequent local discomfort. No serious adverse events. No GBS signal. Well tolerated during coadministration with other vaccines.
Recombinant	Comparable to standard IIV despite higher antigen dose. Minor increase in chills and injection site redness. Safe for use during pregnancy.
Live attenuated	Excellent safety in children. Mild respiratory symptoms. Contraindicated in severe immunocompromise and children <2 years. No safety concerns in children with asthma and well-controlled HIV.

Immunogenicity

Typically, the immunogenicity of influenza vaccines is measured by neutralising antibody responses against haemagglutinin, using haemagglutinin inhibition assays (HAI) or neutralisation assays, and is infrequently compared directly with clinical protection. For the most part, studies define seroprotection by HAI titres (≥1:40) and non-inferiority as a geometric mean titre ratio of over 1 or 1.5. Few studies have assessed T cell response and memory induced by influenza vaccines. The mechanisms generating immunity against influenza vaccines and influenza virus are more complex than neutralising IgG antibody against haemagglutinin alone. Anti-neuraminidase responses also function in influenza immunity. Factors such as prior exposure, interferon signalling and innate immune responses are also likely to play a role in vaccine effectiveness. Findings are summarised in Table 2.

Cell-based influenza vaccines induce similar antibody responses to egg-based influenza vaccines. Limited recent studies describe the immunogenicity of cell-based IIV and making direct comparison between cell-based and egg-based influenza vaccines is problematic, since the quantification of antibody levels depends on which virus strains are used in both the assay and the vaccine.

Both adjuvanted and high-dose influenza vaccines induce a strong humoral response with higher antibody titres than induced by standard-dose vaccines. Evidence suggests differences in the immunological mechanism between responses to these vaccines.

Recombinant influenza vaccine has improved immunogenicity against haemagglutinin compared with standard IIV. It is unclear whether the absence of neuraminidase from this vaccine enhances or diminishes anti-influenza immunity. Immunogenicity comparisons can only indicate differences in the humoral response to a vaccine, not whether improved antibody responses translate into greater clinical effectiveness against influenza or reduce severity of disease.

Evidence for immunogenicity of LAIV is limited, since measuring serum HAI titres is less relevant, and mucosal IgA and IgG responses are most likely to influence immunogenicity and efficacy of this vaccine.

Table 2: Comparison of immunogenicity of enhanced influenza vaccines.

Vaccine Type	Summary
Cell-based	Comparable antibody responses to egg-based IIV. May activate broader immune signalling (e.g., interferon).
Adjuvanted	Enhances antibody titres modestly (GMTR ~1.5). Boosts both haemagglutinin and neuraminidase immunity. No clinically relevant interference observed when coadministered with other vaccines.
High-dose	Strong humoral response, especially A/H3N2. Most effective in older or immunocompromised adults. May be considered for some severely immunocompromised groups.
Recombinant	Induces strong IgG and CD4+ T-cell responses. Comparable antibody titres to cell or egg-based IIV. Contains a high dose of pure haemagglutinin. Less glycosylation allows improved epitope recognition.
Live attenuated	Stimulates mucosal (IgA) and cellular immunity. Traditional HAI titre assessments less relevant. Effectiveness not dependent on serum IgG.

Effectiveness and efficacy

Reflecting lower immunogenicity, standard influenza vaccine effectiveness is typically less in adults aged 65 and over than in younger age groups. See Table 3 for comparisons between enhanced vaccines.

Efficacy and effectiveness studies of influenza vaccines assess a range of outcomes across various study designs. Outcomes include laboratory-confirmed influenza-like illness (ILI) with differing definitions for ILI; respiratory illness; hospitalisation for influenza or pneumonia; all-cause hospitalisation; cardiorespiratory events; pneumonia; influenza-associated hospital admission; influenza-related medical encounters; and influenza-associated mortality. Study types include randomised controlled clinical trials (RCT), or retrospective, prospective and test-negative designed cohort or population studies. Further, effectiveness is also assessed over a range of seasons with differing circulating virus and is affected by how well the vaccine virus matches the circulating strain. These factors make comparison between studies challenging without head-to-head direct comparisons, although several systematic reviews have been conducted. Additional independent, real-world effectiveness data is emerging with wider use of enhanced vaccines in influenza immunisation programmes.

The majority of the evidence reviewed did not support a clear advantage of cell-based IIV over the traditional egg-based formulation. While data remain inconclusive regarding the absolute superiority of standard cell-based vaccines, even modest gains in effectiveness—between 5% and 10%—could contribute meaningfully to reducing influenza transmission and impact during winter seasons. More recent data from the US showed that the cell-based influenza vaccine was approximately 20% more effective against symptomatic illness in individuals aged 6 months to 64 years, and was predicted to be able to avert an additional 2 million influenza cases.

The protective benefits of influenza vaccination in older adults can be improved with adjuvanted or high-dose influenza vaccines (improving effectiveness by 10 to 30%), particularly against severe

influenza outcomes such as hospitalisation and death, and among those with comorbidities or frailty. Either vaccine is equally superior to standard vaccine.

Comparative studies found recombinant influenza vaccine to be more protective than cell-based IIV in adults younger than 60 years against influenza infection, but data is limited in older adults and those with underlying medical conditions.

LAIV is at least as effective as IIV against influenza infection and severe illness in children. Vaccination of children can also help curb the spread of infection, potentially boosting the overall effectiveness of influenza vaccines in older adults and thereby further improving the modest gains provided by enhanced influenza vaccines in older age groups.

Table 3: Comparison of effectiveness of enhanced influenza vaccines

Vaccine Type	Summary
Cell-based	Modest gains in ages 6 months – 64 years. No significant advantage in ≥65 years. Helps reduce risk in egg-adaptation mismatch seasons and to avert more influenza cases and hospitalisations.
Adjuvanted	Better outcomes in older, frail, and comorbid populations. Reduces hospitalisation, myocardial infarction, stroke.
High-dose	Demonstrated reduction in mortality and complications during strain mismatch seasons. Effective across older adult cohorts. Similar effectiveness to aIIV.
Recombinant	Modest benefit in adults <65 years, especially against A strains. Limited data in ≥65 years.
Live attenuated	62 – 75% effectiveness in children against infection and hospitalisation. Shows herd immunity potential and may reduce the incidence of secondary bacterial infections. Intranasal administration increases acceptability and coverage.

Conclusions

The key finding from this review is that receiving any vaccine is better than not being vaccinated, even when the effectiveness is compromised by a weaker immune response.

Influenza vaccination already confers substantial health benefits, leading to reductions in acute respiratory illness, secondary bacterial infections, cardiovascular events and functional decline, and reduced hospitalisation and mortality. While the relative improvement in vaccine effectiveness provided by these 'enhanced' influenza vaccines may be modest, they build on this strong foundation—amplifying protective outcomes and further reducing the seasonal disease burden on the health system and individuals.

Enhanced vaccines can help to improve immunogenicity, but these vaccines do not overcome the challenges of matching with the circulating strains. The match with circulating strains can be improved somewhat with cell-based and recombinant vaccines, but currently still relies on predicting next season's strains several months out. This is especially evident during seasons dominated by influenza A strains (particularly A/H3N2 and to a lesser extent A/H1N1), which are at risk of egg adaptation resulting in reduced vaccine effectiveness. Using cell lines could also enable more responsive production to circumvent any antigenic changes in circulating virus or emergence of novel pandemic strains.

In older adults, the use of adjuvanted and high-dose influenza vaccines provide additional benefit, particularly against more severe illness and death, by improving the immunogenicity of the standard vaccines. Evidence is limited around the use of recombinant vaccine in older adults or special groups.

LAIV is a suitable option for children, particularly when administered widely through school and preschool age groups. As an intranasally administered vaccine, coverage is likely to be improved over needle-based administration. It is more acceptable for those nervous of needles and does not require an authorised vaccinator to administer it. Vaccine options for infants and young children under 2 years of age are limited to egg- or cell-based IIV.

Recommendations for the New Zealand immunisation programme

Derived from the evidence, presented below are recommendations for the influenza immunisation programme. For summary see Table 4

- Encourage wider uptake of influenza vaccination with the available vaccines, across all age groups, including children aged under 5 years.
- Recommend adjuvanted (currently available for use) or high-dose (not yet approved for use) influenza vaccines for older adults, particularly with comorbidities, and especially for those with a high degree of frailty such as those living in residential aged-care facilities or requiring in-home carers. Once regulatory approval is achieved, cell-based adjuvanted vaccine could improve effectiveness further.
- Recombinant influenza vaccine (not yet approved for use in NZ) would be suitable for anyone currently eligible for funded vaccine, particularly those who are moderately immunocompromised.
- LAIV is highly recommended for children, given universally as part of a preschool and school-based programme. Unfortunately, this vaccine is not yet approved for use in New Zealand. Improvements in access to funded influenza vaccine are required in the meantime for all children.

Table 4: Recommended seasonal influenza vaccine use, by population group

Population group	Most suitable vaccine(s)
Children (aged 6 months – 23 months)	*Inactivated influenza vaccine (egg or cell-based IIV) – not specifically included in this review*
Children (2–17 years)	Live attenuated (LAIV) — intranasal, highly effective, well tolerated
Adults <65 years	Cell-based (IIVc), recombinant (RIV) — modestly improved effectiveness
Adults ≥65 years	Adjuvanted (aIIV) or high-dose (hd-IIV) — both enhance protection in frailty and those with comorbidity
Immunocompromised adults	Adjuvanted and high-dose — safe and immunogenic; LAIV contraindicated
Pregnant people	Standard IIV, recombinant RIV — both shown to be safe and effective. No data reviewed for cell-based IIV.

Introduction

This review of evidence aims to evaluate the role that different seasonal influenza vaccine formulations may have in the prevention of influenza in Aotearoa New Zealand (NZ). 'Enhanced' inactivated influenza vaccines (IIV) include high-dose, adjuvanted, cell-based and recombinant subunit formulations. It will also briefly review recent evidence for live attenuated influenza vaccine (LAIV), particularly in children aged from 2 years.

This is not a systematic review, and cost-benefit analyses are not included. It will include vaccines that are not yet approved for use in New Zealand. The recommendations and interpretation of data are solely that of the author.

Challenges of comparing seasonal influenza vaccines

Comparing influenza vaccines is complex. Immunogenicity is measured in several ways, but most studies depend on serum antibody levels to assess seroprotection. These are measured primarily by haemagglutinin inhibition assay (HAI) (seroprotective titres ≥1:40), neutralising antibody (seroprotection at titres ≥1:10) and seroconversion rates. Virus strains used in these assays can influence the outcomes – for example, using the same cell-based virus strain as used in the vaccine production may produce different results than using virus strains contained in the egg-based vaccine. Few studies evaluated cellular responses.

Immunogenicity comparisons can only indicate differences in the humoral response to a vaccine, not whether improved antibody responses will make the vaccine more clinically effective against influenza or reduce severity of disease.

Efficacy and effectiveness studies of influenza vaccines assess a range of outcomes, different study designs and controls. For example, outcomes include laboratory-confirmed influenza-like illness (ILI) with differing definitions for ILI; respiratory illness; all-cause hospitalisation; cardiorespiratory events; pneumonia; influenza-associated hospital admission; influenza-related medical encounters; and influenza-associated mortality. Further to this, effectiveness is also assessed against different influenza strains and is affected by how well the vaccine virus matches the circulating strain.

Overview of influenza vaccines

The Holy Grail is a 'universal' influenza vaccine that targets conserved epitopes on all influenza virus strains, such that it does not require annual adjustments and can induce long lasting immunity across all age groups. In the absence of the elusive universal influenza vaccine and with the aim of improving the immunogenicity and clinical effectiveness of seasonal influenza vaccines, a range of technologies have been employed and some of these vaccine formulations have been marketed. More influenza vaccines are in clinical development, particularly mRNA-based vaccines, but are not described here.

Challenges are still faced when it comes to matching the vaccine influenza strains with the circulating influenza strains. This is primarily due to the long production timeline for the current seasonal influenza vaccines. Production commences at least six months prior to the season, typically around October in the Southern hemisphere. Recommendations around the viral composition of the seasonal

influenza vaccine are based on data collated by the WHO's Global Influenza Surveillance and Response System (GISRS), which predicts the predominant strains for the Southern and Northern hemisphere influenza seasons. Influenza A viruses are classified by surface antigens into 18 haemagglutinin (H) and 11 neuraminidase (N) subtypes, eg H3N2 or H1N1, and further identified by a strain designation. As a result, the current vaccines are only as good as the prediction and accuracy of the manufacturing process to produce vaccine virus strains. Furthermore, circulating strains can undergo antigenic drifts prior to or during a season resulting in a less effective vaccine due to a mismatch with the mutated virus.

Vaccines reviewed:

- Cell-based inactivated influenza vaccine
    - Brand name: Flucelvax® (CSL Seqirus)
    - Abbreviations: trivalent (TIVc) or quadrivalent (QIVc)
- MF59® adjuvanted inactivated influenza vaccine
    - Flud ® and Fluad® Quad (CSL Seqirus)
    - Abbreviations: trivalent (aTIV) or quadrivalent (aQIV), cell-based (aTIVc)
- High-dose inactivated influenza vaccine
    - Fluzone® High-Dose (Sanofi)
    - Abbreviations: trivalent (hd-TIV) and quadrivalent (hd-QIV)
- Recombinant influenza vaccine
    - FluBlok® or Supemteck® (Sanofi)
    - Abbreviations: trivalent (RIV3) and quadrivalent (RIV4)
- Live attenuated influenza vaccine
    - FluMist® or Fluenz® (AstraZeneca)
    - Abbreviation: LAIV

Inactivated influenza vaccines

Inactivated influenza vaccines (IIV) have been used since the 1940s. These are the most widely used types of influenza vaccine, since they are non-live vaccines and can safely be given to infants and young children, during pregnancy, to frail elderly and to people with compromised immune function. Most IIV are subunit or split virion types. These vaccines are designed to induce neutralising antibody to prevent infection by blocking the attachment of the virus to the cells of the respiratory tract. Both trivalent and quadrivalent forms are used, containing two influenza A strains and one (TIV) or two (QIV) influenza B strains, respectively.

Since standard influenza vaccines are less effective in those with weaker immune response, in particular older adults but also in young children, enhancements have been made to IIV, with higher doses of antigen and with the inclusion of adjuvant (see below for further details).

Egg-based influenza vaccines

Traditionally, influenza virus for vaccines is mass-produced in millions of embryonated hens' eggs (in 2023, CSL Seqirus estimated its usage to be 100 million eggs per year worldwide).[1] The virus is then isolated and inactivated chemically. Either the whole virus is disrupted and purified (split virion vaccine) or the disrupted virus is purified further to isolate the surface proteins (subunit vaccine). Each subunit vaccine has a defined quantity of strain-specific haemagglutinin, the main active ingredient, and some neuraminidase (which is not routinely measured). As technology for purifying influenza virus has improved, the reactogenicity of the influenza vaccines has been reduced making them more

suitable for use in young children. Subunit vaccines are associated with less reactogenicity than the split virion vaccines containing the whole virus.

Mutations can occur to the vaccine virus as the virus adapts to replicating in eggs, known as egg-adaptation. These can result in a potential mismatch between the vaccine virus and the circulating virus antigens, producing lower affinity antibodies and reducing vaccine effectiveness. Experts in Europe estimated that egg-adaptation can reduce vaccine effectiveness by 4% – 16%.[2] This is particularly seen with the A/H3N2 strains, and to a less extent, with A/H1N1.

Cell-based influenza vaccine

A mammalian cell line, Madin-Darby canine kidney (MDCK) cells, is used instead of embryonated hens' eggs to produce cell-based IIV (IIVc). The influenza viruses are seeded and grown in cell culture, then inactivated and purified in the same way as for egg-based vaccines. The commercially available cell-based vaccine, Flucelvax (Seqirus) is a subunit inactivated influenza vaccine.

Key advantages of this method of producing influenza virus are:

- it does not require large numbers of hen's eggs
- large volumes of cell culture can produce large quantities of virus comparatively quickly
- cell-lines and seed virus can be stored in frozen cell banks to scale-up as required.

This is beneficial if there is a significant change in circulating strains or in the case of an emerging, novel (pandemic) strain. Another key advantage is that the risk of mutations occurring in virus during manufacture is reduced, therefore, where the strain prediction has been accurate, vaccine effectiveness is maintained.[3]

Adjuvanted influenza vaccine

The addition of adjuvant to IIV is designed to boost vaccine immunogenicity and potentially enhance the effectiveness (aIIV; Fluad Quad®, Seqirus), particularly for use in older people and also in infants and young children. This vaccine utilises MF59®, a squalene-based oil-in-water emulsion adjuvant, which has been incorporated in influenza vaccine candidates since the 1990s. The vaccine virus is produced using the standard egg-based IIV method and then combined with the MF59 adjuvant. Clinical development of a cell-based, adjuvanted, influenza vaccine is underway by CSL Seqirus.

High-dose influenza vaccine

Another approach to increase the immunogenicity of IIV, and thereby effectiveness, is to increase the amount of antigen given per dose. Compared with the standard egg-based IIV which contain 15µg of haemagglutinin per virus strain per dose, high-dose influenza vaccine (hd-IIV; Fluzone®, Sanofi) contains 60µg haemagglutinin per virus strain per dose.

Recombinant influenza vaccines

Using recombinant DNA technology, influenza haemagglutinin can be produced synthetically from a genetic sequence rather through the propagation of influenza virus in eggs or cell-lines. By producing a recombinant protein subunit, the vaccine antigen does not need to be purified from large quantities of inactivated virus and can be rapidly upscaled. This antigen will therefore have a precise match to the surface antigen on the predicted target strains. Recombinant influenza vaccine (RIV) is likely to be important in case of an influenza pandemic, by allowing responsive and rapid production of vaccine antigen. A limitation occurs when the predicted strain mismatches the circulating strain. Furthermore,

it is currently unclear what role other viral antigens, such as neuraminidase, play in immunity but they may provide cross-protection and long-term immunity.[3] Recombinant influenza vaccine was first approved for use by the FDA in the US in 2013 from age 18 years (FluBlok®, Sanofi) and in Europe in 2020 from age 9 years (Supemteck®, Sanofi).

Live attenuated influenza vaccine

Live attenuated influenza vaccine (LAIV) contains cold-adapted influenza virus. The vaccine virus preferentially replicates at 25°C, with limited replication in in the cooler nasal mucosa (at around 33°C), and not in the lower respiratory tract as for wild-type seasonal influenza virus. It is administered by intranasal spray rather than intramuscular injection. To produce the target strain virus, the cold-adapted 'master donor virus' backbones (A/Ann Abor/6/60 and B/Ann Arbor/1/66) and the seasonal influenza strain of interest are combined into a reassorted, attenuated virus. Reverse genetics co-transfection is routinely used to produce seed virus: six DNA plasmids bearing genes from the attenuated virus and two plasmids with genes for HA and NA from circulating influenza virus are used to transfect cells to produce an attenuate reassortant vaccine virus. This reassorted virus is then used to seed embryonated hens' eggs in the manufacture of the vaccine.[4] This vaccine contains the whole live attenuate virus rather than subunits, inducing a broader, mucosal immune response.

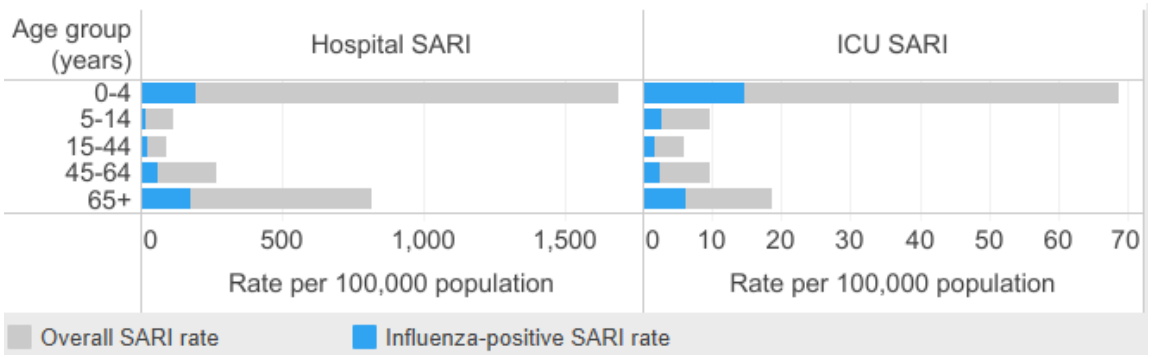
As with IIV, LAIV are dependent on accurate prediction of the next season's circulating influenza strains and mismatches can occur that result in reduced effectiveness. Cell-based LAIV are in development.[5]

The AstraZeneca vaccine (Fluenz® or FluMist®) is approved for use in Europe and North America for children aged from 2 years to 18 years, and in North America for adults up to age 49 years. Regulatory approval for a Southern hemisphere formulation is being sought in Australia. Two doses are administered at least 4 weeks apart. LAIV have also been used since 1987 in Russia, based on different master donor viruses (A/Leningrad/134/17/57 (H2N2) and B/USSR/61/69), and has more recently been manufactured in India.[6]

Epidemiology

The burden of influenza disease is greatest in young children aged under 4 years and in adults aged 65 and over (Figure 1). In Aotearoa New Zealand, people of Pacific or Māori ethnicity are also at higher risk from influenza hospitalisation than those of other ethnicities, as are those living in areas of high socioeconomic deprivation. Although influenza transmission was disrupted in 2020 and 2021, due to non-pharmaceutical interventions during the COVID-19 pandemic, a large spike in cases was seen earlier than usual in 2022 when the international borders were re-opened. The influenza epidemiology returned to a pre-pandemic pattern in 2024 with the winter season peak in mid-late July and with a moderately high severe acute respiratory illness (SARI) hospitalisation rate.

Figure 1: Cumulative hospitalisation rates with severe acute respiratory illness (SARI) by age, influenza positive, 2024 (source: ESR/PHF Science)



During the 2024/2025 winter in the Northern Hemisphere, many countries reported high seasonal influenza activity. Cases of influenza in the UK peaked in late December 2024.[7] The US saw the high influenza activity across most states in early February 2025, with the highest severity of disease being seen across all age groups since 2017/2018 season. As of 3 May 2025, there had been 27,000 influenza-associated deaths including 226 paediatric deaths across the whole season.[8]

See the PHF Science (formerly ESR) Respiratory illness dashboard for details of current and past seasons https://www.phfscience.nz/digital-library/respiratory-illness-dashboard/#respdashboard

International recommendations for enhanced influenza vaccines

The following provides a comparison with other countries between influenza vaccines funded and/or recommended in NZ to identify in which groups standard and enhanced influenza vaccines are being used.

No confirmed detections of B/Yamagata were reported after March 2020.[9, 10] Hence, from 2025, most manufacturers will return to a trivalent vaccine as the WHO has concluded that B/Yamagata lineages are no longer in circulation, therefore not warranted in the seasonal influenza vaccines. However, the following is based on available information at the time of this review, and for some, QIV vaccines were still available because manufacturers had not yet transitioned from QIV to TIV.

For a summary see Table 7.

Australia

Influenza vaccination is recommended for everyone from 6 months of age. It is funded for all children aged 6 months to <5 years and all adults aged 65 years and over. Funded vaccine is also available for people aged 5 to <65 years who are:

- Aboriginal and Torres Strait Islander
- have certain medical conditions
- are pregnant.

Adjuvanted or high-dose QIV is preferred over standard vaccine for those aged ≥65 years; where available, there is no preference between adjuvanted or high-dose vaccine in this age group. For 2025 season, cell-based QIV is available from age 6 months. The Australian Technical Advisory Group on Immunisation (ATAGI) made no preference recommendation between QIV or TIV. See Table 5 for influenza vaccine availability in Australia.

Table 5: Seasonal influenza vaccines registered and available for use in Australia in 2025, by age (source ATAGI)

Vaccine / Registered age group	Vaxigrip Tetra 0.5 mL (Sanofi)	Flucelvax Quad 0.5 mL (CSL Seqirus)	FluQuadri 0.5 mL (Sanofi)	Afluria Quad 0.5mL (CSL Seqirus)	Influvac Tetra 0.5 mL (Viatris)	Fluad Quad 0.5 mL (CSL Seqirus)	Fluzone High-Dose 0.7 mL (Sanofi)
6 months to <5 years	✓	✓	✓	X	✓	X	X
≥5 to <60 years	✓*	✓*	✓	✓	✓	X	X
≥60 to <65 years	✓*	✓*	✓	✓	✓	X	✓
≥65 years	✓	✓	✓	✓	✓	✓	✓

Ticks indicate age at which a vaccine is registered and available. White boxes indicate availability for free under the NIP.
* NIP funding only for Aboriginal and Torres Strait Islander people, pregnant women and people who have certain medical conditions.

Source: https://www.health.gov.au/resources/publications/atagi-statement-on-the-administration-of-seasonal-influenza-vaccines-in-2025-0

Canada

Influenza vaccination (TIV or QIV and LAIV) is recommended for everyone from age 6 months.[11]

The Province of Ontario is the only province with a *Universal Influenza Immunization Program* that provides publicly funded influenza vaccine to everyone who lives, works or attends school in Ontario,

from aged 6 months and over. Pharmacies approved to provide this program can administer influenza vaccine to individuals aged 2 years and over.

Source: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-10-influenza-vaccine.html

United States (US)

Influenza vaccination is recommended for anyone aged from 6 months. Vaccines are generally funded through insurance in the US, or if eligible, through the CDC's Vaccines for Children programme. As a result, a larger variety of vaccine types with broader recommendations are available in the US than in countries where vaccines are offered through publicly funded National Immunisation Schedules. For the 2024 – 2025 season, all vaccines were trivalent (A/H1N1pdm09, A/H3N2 and B/Victoria-lineage). The cell-based and recombinant vaccines contained the same virus strains, but these differed from the egg-based ones.

Sources: https://www.cdc.gov/flu/hcp/acip/; https://www.cdc.gov/flu/season/2024-2025.html

United Kingdom (UK)

In the UK, different types of influenza vaccine are available and recommended to different groups (see Table 6). The Joint Committee for Vaccination and Immunisation (JCVI) makes recommendations for each season.

Table 6. Summary of influenza vaccines recommended by JCVI for 2025 – 2026 season (UK Health Security Agency)

IIV – inactivated influenza vaccine; aIIV – adjuvanted; IIV-HD – high-dose; IIVr – recombinant; IIVc – cell-based; IIVe – egg-based; LAIV – live attenuate influenza vaccine

Age or risk group	Vaccine preference	If the preferred vaccine is unavailable
Over 65 years of age	aIIV, IIV-HD, IIVr	IIVc
18 to 64 years in a risk group	IIVc, IIVr or aIIV (in those aged 50 to 64 years) or IIV-HD (in those aged 60 to 64 years)	IIVe
2 to under 18 years	LAIV	IIVc
2 to under 18 years but unable to have LAIV	IIVc	IIVe
6 months to under 2 years in a risk group	IIVc	IIVe

Note: LAIV is the vaccine of choice for children aged 2 to 17 years.

Source: https://www.gov.uk/government/publications/flu-vaccines-2025-to-2026-jcvi-advice/jcvi-statement-on-influenza-vaccines-for-2025-to-2026

Table 7. International influenza vaccine recommendations (Northern Hemisphere 2025/2026 and Southern Hemisphere 2025 seasons)

Country	Standard IIV / IIVc		LAIV	Adjuvanted or high dose		Recombinant	
	age group	comments	age group	age group	comments	Age group	comments
New Zealand	Aged from 6 months All aged from 65 years	QIV funded for certain medical conditions and in pregnancy QIV funded	Not available	≥65 years	aQIV, not funded HD-IIV not available	Not available	
Australia	All children aged 6 months – 5 years	QIV funded	Not available	ATSI ≥60 years All ≥65 years	hd-QIV, funded aQIV, funded	Not available	
	All ATSI people aged from 6 months	QIV and QIVc, funded					
	All aged ≥65 years	QIV and QIVc, funded					
	Ages 5 – < 65 years	QIV and QIVc, funded for certain medical conditions and in pregnancy					
Canada	All infants 6–23 months	QIVc QIV authorised, not recommended <3 years	Most children aged 2-17 years	All infants 6–23 months	Paediatric aTIV	60-64 years	RIV4 or QIVc
	Children aged 2–17 years with immunocompromise or severe asthma	QIVc or QIV, if LAIV is contraindicated		≥65 years	hd-QIV or aTIV	≥65 years	RIV4 preferred over QIVc
	All aged 18-59 years	QIV or QIVc (including pregnant)	18–59 years (not pregnancy)			18–59 years (including pregnant)	RIV4 or QIVc
US	Anyone from age 6 months	TIV	Ages 2 – 49 years	Aged ≥65 years	aTIV or hd-TIV	Ages from 6 months Age from 18 years	TIVc RIV3
UK	All infants 6m - <2 years All aged ≥2 years	QIVc or QIV funded QIV, if QIVc not available and contraindicated LAIV	all children age ≥2 years	All adults aged ≥65 years	aQIV or HD-IIV	Ages ≥65 years	RIV, if preferred
	At-risk adults 18-64 years (including pregnant)	QIVc, or QIV if other options unavailable		All adults at risk aged 50-64 years All adults at risk aged 60-64 years	aQIV hd-QIV	At-risk adults 18-64 years (including pregnant)	RIV4

Abbreviations: IIV – inactivated influenza vaccine; QIV - Quadrivalent inactivated influenza vaccine (standard, egg-based); aQIV – adjuvanted; hd-QIV – high-dose QIV; QIVc – cell-based; RIV – recombinant; LAIV – live attenuated influenza vaccine; ATSI – Aboriginal and Torres Strait Island peoples; RIV – recombinant influenza vaccine; TIV – trivalent influenza vaccine

Review of recent literature

The following will review the recent literature, primarily published between January 2019 and July 2025, to assess the evidence for the safety, immunogenicity and effectiveness of enhanced seasonal influenza vaccines in the New Zealand context. It will not review the cost-benefit analyses. It is not a systematic review. This follows on from a review of evidence of influenza conducted by the Immunisation Advisory Centre in 2022, which primarily focussed on influenza control through vaccination of children.[12]

Cell-based inactivated influenza vaccines

Cell-based influenza vaccines use viruses grown in mammalian cell cultures instead of chicken eggs. This method avoids the mutations that can occur when the vaccine virus adapts to grow in eggs, which can cause mismatches between the vaccine and the wild-type strains, potentially reducing vaccine effectiveness in certain seasons. The following will compare the safety, immunogenicity and effectiveness of cell-based inactivated influenza vaccine and, where possible, compare these with those of standard egg-based IIV. For details of the studies see Table 8.

Before considering the literature around vaccine effectiveness of cell-based inactivated influenza vaccines, the source of the vaccine virus needs to be taken in to account for two reasons.

1. As the vaccine technology developed, only some of the virus strains used in the QIVc vaccine had changed from egg-based to cell-based manufacture, such that during the 2018/19 season only A/H3N2 and influenza B strains were produced in cell-lines but not A/H1N1; from 2019/2020, cell-based strain A/H1N1 was included.
2. Secondly, as indicated in some of the literature, production has transitioned from using a seed virus that was initially established in eggs to fully cell-based seed strains produced in MDCK cells.

More recently, the vaccine has used fully cell-line-based vaccine viruses. Therefore, further studies are required using purely cell-grown virus to confirm whether complete avoidance of egg-adaptation can improve effectiveness of cell-based influenza vaccines.

Safety

Cell-based vaccines are well tolerated in adults and have similar safety profile to egg-based influenza vaccines. A single systematic review considered the safety of cell-based IIV (trivalent TIVc or quadrivalent QIVc) in adults aged from 18 years.[13] One reviewed study noted that, as seen with other vaccines, adverse reactions were more common in younger than older adults (ages 18 – 61 years versus ages over 61 years).[13]

Enhanced passive surveillance in Italy did not identify any safety signals of concern over three influenza seasons.[14] The rates of reported adverse events decreased significantly over the study period, from 1.75% in 2019/20 to 0.48% and 0.40% in 2020/21 and 2021/22. Vaccine was administered at ages 9 years and over in 2019/20 and from age 2 years thereafter, however, coverage in paediatric groups was low. One case of anaphylaxis was considered vaccine related. These findings confirmed the safety profile presented in the product information.[14]

No clinically meaningful differences in adverse events were seen between cell-based and egg-based QIV in the US.[15] A phase 3 randomised controlled trial (RCT) compared cell-based QIVc with the licensed egg-based QIVe in 2,402 young children aged 6 to 47 months (approx. one third were aged 6 – 23 months and two-thirds aged 24 – 47 months).[15] The adverse event profile was consistent with that of other QIVs in this age group and with QIVc in older children.[15-17] Another RCT, conducted across three influenza seasons in eight countries, found that the safety profile of QIVc in children aged 2 to under 18 years was similar to that of a meningococcal ACWY vaccine comparator. Around a half of the participants in each group (51.4% vs 48.6%) reported solicited local or systemic adverse events within 6 hours and 7 days after vaccination.[16]

A post-marketing surveillance study in Italian healthcare workers confirmed a good safety profile of QIVc through active reporting of adverse events following immunisation (AEFI). Most frequently reported AEFI were local reactions, predominantly pain at injection site, general malaise, some fever and gastrointestinal symptoms. Females and younger adults reported AEFI more frequently than males and older adults.[18]

Summary

The safety and reactogenicity profile of cell-based inactivated influenza vaccine is like other inactivated influenza vaccines. No safety concerns have been identified in any age group from 6 months. Anaphylaxis, as with all other vaccines, can occur very rarely.

Immunogenicity

There are few recently published studies describing the immunogenicity cell-based influenza vaccines.

Similar immune responses were seen between cell-based QIV and the US-licensed egg-based QIV in young children aged 6 – 47 months.[15] In the immunogenicity cohort of a phase 3 RCT, 1,092 children received QIVc and 575 received QIVe during the 2019/2020 influenza season in the US. The findings showed that the geometric mean titre ratio (GMTR) between QIVe : QIVc did not exceed 1.5 and seroconversion rate differences (QIVe - QIVc) did not exceed 10% for the four virus strains.[15]

Despite no significant differences in antibody responses (seroconversion rate, seropositivity or mean fold-rise) in children and young adults aged 4 – 20 years (median age 14 years), QIVc induced greater interferon-gamma (IFN-γ) signalling and innate immune activation than QIVe.[19, 20] The children who seroconverted to at least one influenza vaccine strain had correspondingly higher IFN-γ signalling than those who did not seroconvert, regardless of the vaccine type. These clinical trial data suggested that different arms of the immune system, beyond antibody protection, may play a role in improving the effectiveness of influenza vaccines.[20]

Another RCT found that age and prior season vaccination played a role in the immune response of children and young adults (aged 4 to 21 years) to both QIVc and live attenuated influenza vaccine (LAIV).[21] The haemagglutinin inhibition (HAI) assay and immunoglobulin isotype responses were higher in the QIVc group than LAIV, with significant increases in IgG but not IgM or IgA. Younger children had highest responses to LAIV. Prior exposure to LAIV was associated with a greater response to the current season QIVc.[21]

Summary

Cell-based influenza vaccines appear to induce similar antibody responses to egg-based influenza vaccines. Demonstrating immunogenicity appears to be dependent on the source of the virus strain

used in both the assays and the vaccines. The mechanism of immunity to influenza vaccines and influenza virus is more complex than neutralising IgG antibody against haemagglutinin. Factors such as prior exposure, interferon signalling and innate immune responses are likely to play a role in vaccine effectiveness.

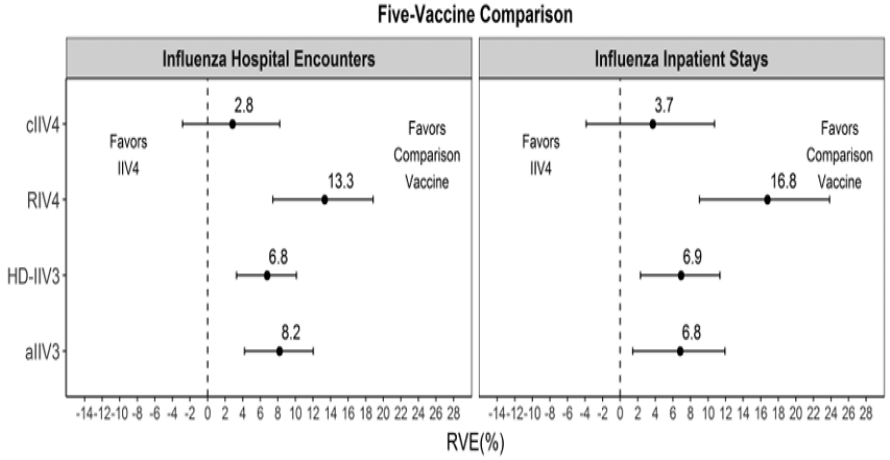
Efficacy and effectiveness

Coleman et al (2023) conducted a systematic review of primarily Seqirus-funded studies to compare the efficacy and effectiveness of cell-based with egg-based inactivated influenza vaccines over three seasons (2017 – 2020).[22] Overall, the pooled relative effectiveness (rVE) of QIVc compared with standard dose IIVe or no vaccination was 8.4% (95% CI 6.5 – 10.2%) against any influenza-related medical encounters (IRME) and/or laboratory-confirmed influenza. For people aged 4 – 64 years, QIVc was consistently more effective relative to egg-based vaccines over three seasons. Re

Several Seqirus-funded studies have examined the relative effectiveness of QIVc and the use of QIVc in a range of populations. Examples are given below (including studies also included in the Coleman systematic review above[22]).

- Individuals aged from 4 years with at least one underlying health conditions: rVE 13.4% [11.4-15.4%] against IRME.[23]
- QIVc was associated with a greater reduction (of around 12%) in IRME of children aged 4 – 17 years than QIVe. But with less than 1% of children being hospitalised, no additional benefit could be shown for inpatient hospitalisation.[24]
- Hospitalisation data during 2016/17 and 2017/18 seasons, with high A/H3N2 predominance, indicated pooled effectiveness against A/H3N2 hospitalisation across both years was low (<25%) for QIVc, despite a good match with the vaccine strain and the same virus strain being used across both seasons. This was thought to be due to egg-adaptation of the seed virus.[25]
- For adults aged 65 years and over, QIVc was not significantly different from standard QIVe against influenza-related hospital encounters when A/H1N1 was the predominant strain (see Figure 2).[26] Seasonal variation in predominant influenza types (ie A/H1N1) and egg-adaptation of vaccine virus likely influenced these results.[22]

Figure 2: Comparison of relative vaccine effectiveness (RVE) against influenza-related hospitalisation for four types of influenza vaccine: cIIV4 – cell-based vaccine; RIV4 – recombinant influenza vaccine; HD-IIV3 – high dose trivalent vaccine; aIIV3 - adjuvanted trivalent vaccine (Izurieta, et al 2021)



- QIVc provided protection to healthy children and adolescents against influenza during a phase 3 clinical trial.[16] The RCT, conducted over three influenza seasons across eight countries, compared influenza incidence in 4,514 healthy children aged 2 to under 18 years (median age 8.8 ± 4.1 years) who were randomised to receive either QIVc or a meningococcal (MenACWY) vaccine. The incidence of laboratory-confirmed influenza was greater in the control group than the influenza vaccine group (16.2% vs 7.8%). Vaccine efficacy against any influenza strain was 54.7% (95% CI 45.7 – 62.1%) and for antigenically matched strains against culture-confirmed influenza was 63.6% (53.6 – 71.5%). The highest efficacy of 80.7% (69.2 – 87.9%) was against A/H1N1 influenza.[16]
- Across three seasons in the US (2017 – 2020), superior effectiveness for cell-based over egg-based QIV was shown retrospectively against test-confirmed influenza. Approximately 10% of patients aged 4 – 64 years received QIVc and 90% received QIVe.[27] During 2019/2020, in which all four vaccine strains were cell-derived, rVE for QIVe was 10% (2.7 – 16.7%).[27]
- Relatively fewer IRME were also seen retrospectively during the peak of the 2019/20 influenza season for QIVc vaccinated adults aged 18-64 years than those given QIVe (rVE 9.5% (7.9-11.1% any IRME).[28]

An independent systematic literature review reported a lack of high-quality evidence for efficacy and effectiveness for cell-based vaccines in adults. The limited evidence from a single influenza season suggested that effectiveness might be slightly better for cell-based vaccines. However, findings for effectiveness based on three test-negative studies and one cohort study were inconsistent between seasons, outcomes and comparators (egg-based IIV or no vaccination).[13]

A test-negative design study in primary care in Great Britain during the 2022/23 season (A/H3N2 predominant with A/H1N1 cocirculation) reported moderate vaccine effectiveness overall against laboratory-confirmed A/H3N2 across all the available influenza vaccines, except in older adults who mostly received adjuvanted vaccine. In adults aged 18 – 64 years, effectiveness of the influenza vaccines was 37% (21 – 50%) against A/H3N2. Most adults aged under 65 years received QIVc and the effectiveness against all influenza strains was 48% (95% CI 37 – 57%) for those vaccinated with QIVc. Effectiveness was 26% (-32 to 58%) for those vaccinated with QIVe (based on only 19 cases).[29]

Note that vaccination may not have been recorded if given in the workplace and funded vaccine was only available to high-risk adults aged under 65 years.

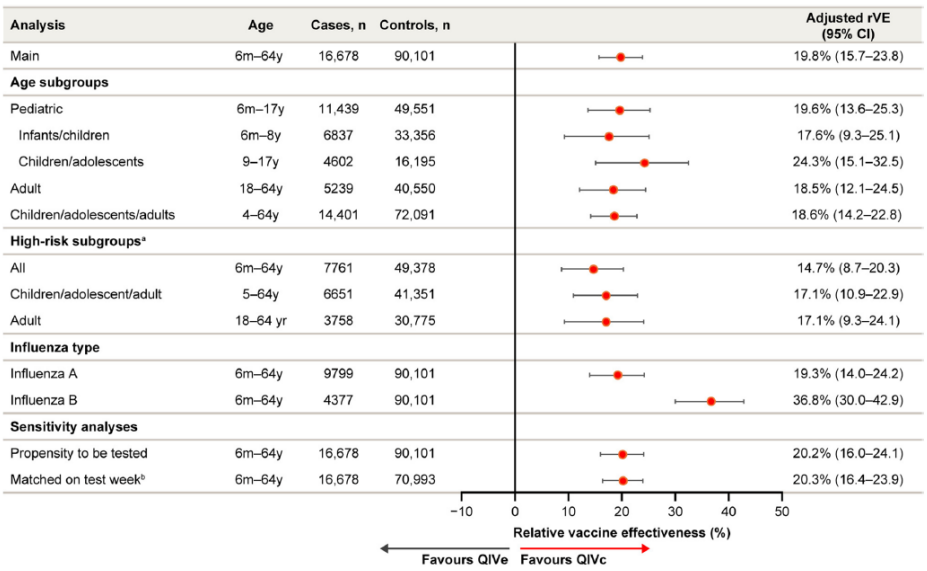
During the same season (2022/23) in California, cell- and egg-based influenza vaccines provided comparable protection against influenza-associated hospitalisation in 848,334 adults aged 18 – 64 years. Comparative effectiveness of QIVc against hospitalisation in adults aged 18 – 49 years was minus 10% (-49.8 to 37.8%) and for those aged 50 – 64 years was 14.9% (-33.8 to 52.1%).[30]

Other studies also found that cell-based vaccines provided improved protection for those aged under 65 years but not for older adults.[28, 31] Both QIVc and QIVe provided protection against myocardial infarction and stroke in adults aged 18-64 years, and QIVc was favoured against myocardial infarction in adults aged 50 – 64 years.[31]

Additional data were published after this review was completed and have been included here. During the 2023/2024 influenza season in the US, the rVE of QIVc was shown to be approximately 20% higher than that of QIVe against symptomatic, test-confirmed influenza in individuals aged 6 months to 64 years.[32] A retrospective analysis using a test-negative design (conducted by Seqirus) included 106,779 individuals. Figure 3 shows the adjusted relative effectiveness across groups of interest. Notably, the study provided evidence of improved effectiveness for QIVc in the paediatric population from 6 months of age.[32]

Overall, influenza vaccination was estimated to have averted millions of symptomatic cases: 7.2 million with QIVe and 9.5 million with QIVc. When a burden-averted model was applied, the incremental benefit of QIVc over QIVe was estimated at an additional 2.3 million symptomatic cases prevented, more than 14,000 hospitalisations, and over 500 deaths.[32]

Figure 3: Relative effectiveness of cell-based versus egg-based QIV in the prevention of test-confirmed symptomatic influenza during 2023-2024 influenza season in the US. (Stein et al 2025, open access)



Analysis	Age	Cases, n	Controls, n	Adjusted rVE (95% CI)
Main	6m–64y	16,678	90,101	19.8% (15.7–23.8)
Age subgroups				
Pediatric	6m–17y	11,439	49,551	19.6% (13.6–25.3)
Infants/children	6m–8y	6837	33,356	17.6% (9.3–25.1)
Children/adolescents	9–17y	4602	16,195	24.3% (15.1–32.5)
Adult	18–64y	5239	40,550	18.5% (12.1–24.5)
Children/adolescents/adults	4–64y	14,401	72,091	18.6% (14.2–22.8)
High-risk subgroups[a]				
All	6m–64y	7761	49,378	14.7% (8.7–20.3)
Children/adolescent/adult	5–64y	6651	41,351	17.1% (10.9–22.9)
Adult	18–64 yr	3758	30,775	17.1% (9.3–24.1)
Influenza type				
Influenza A	6m–64y	9799	90,101	19.3% (14.0–24.2)
Influenza B	6m–64y	4377	90,101	36.8% (30.0–42.9)
Sensitivity analyses				
Propensity to be tested	6m–64y	16,678	90,101	20.2% (16.0–24.1)
Matched on test week[b]	6m–64y	16,678	70,993	20.3% (16.4–23.9)

Summary

The effectiveness of cell-based inactivated influenza vaccine is equivalent to or moderately superior to egg-based vaccines in children and adults aged 4 to 64 years. The current evidence does not

appear to show improved effectiveness in older adults, who are particularly vulnerable to loss in protection when A/H3N2 is predominant and is mismatched due to egg-adaptation.

As with traditional vaccines, the effectiveness continues to vary according to the influenza season, the age of the recipients and how well the vaccine strain matches the circulating strain, regardless of whether egg-adaptation has occurred. Most of the evidence reviewed did not sufficiently demonstrate that standard cell-based vaccine is significantly superior to standard egg-based vaccines. However, small improvements in effectiveness could reduce the spread and burden of influenza during the winter. Very recently published evidence (October 2025) from the US suggests that the use of cell-based IIV improved the overall vaccine effectiveness by around 20% in children from age 6 months and adults (under 65 years), and could avert more symptomatic illness and hospitalisation than egg-based IIV.

Adjuvanted inactivated influenza vaccine

Adjuvants are added to enhance the immunogenicity of standard influenza vaccines. This review will only consider evidence for the seasonal MF59 (squalene oil-in-water-emulsion) adjuvanted trivalent or quadrivalent inactivated influenza vaccines: aTIV (Fluad®) and aQIV (Fluad Quad®, Seqirus). Unless otherwise stated, the formulation of these vaccines will be based on egg-grown vaccine viruses, not cell-based. Other proprietary adjuvants, such as AS03 (GSK) have been used in pandemic influenza vaccines but are not used routinely in seasonal vaccines.

Adjuvanted influenza vaccine has been tested for use in young children[33, 34] but it is not widely approved for this use except in Canada for infants aged 6 months to 2 years (FluAd Pediatric, Seqirus). This review will focus on use in adults aged 65 years and over, or relevant groups such as adults with underlying health conditions and those aged from 50 years. See Table 9 for details of studies reviewed.

Safety

The safety profile of adjuvanted inactivated influenza vaccines (aTIV or aQIV) is well established, with over 20 years of use of MF59® adjuvant. No safety concerns were identified through enhanced passive surveillance over four influenza seasons in Italy with consistent adverse event reporting in adults aged 65 years and over.[35, 36] A systematic review comparing adjuvanted and non-adjuvanted influenza vaccine in adults aged from 18 years found most adverse events to be mild to moderate in severity. These included injection site pain, generalised joint or muscle pain, headache, chills and fatigue.[37]

Coadministration with other adjuvanted vaccines

With more adjuvanted and immunogenic vaccines being used in older adult populations, it is important to consider the safety of their coadministration. A survey of literature found no safety concerns around the coadministration of adjuvanted influenza vaccine with other vaccines, including COVID-19, RSV, zoster and 20-valent pneumococcal conjugate vaccine.[38] Most adverse events were generally mild or moderate and of short duration. Some studies showed a slightly higher reactogenicity with coadministration, but no severe adverse events or no safety signals were reported.

As more vaccines are used in adults and older adults, similar strategies to the infant programme will be required as coadministration becomes routine, particularly for seasonal respiratory infections.[38]

No literature was found that specifically considered coadministration with three or more reactogenic vaccines (ie. combinations of adjuvanted RSV vaccine, mRNA COVID-19 vaccine, recombinant zoster vaccine and adjuvanted influenza vaccine), which may be given to protect older adults against winter illnesses.

No significant differences in safety profiles were seen between groups of older adults who received aQIV coadministered with $AS01_B$ adjuvanted recombinant zoster vaccine (rZV, Shingrix® GSK) in separate limbs during a RCT conducted in the US.[39] In a group of community-dwelling participants aged over 65 years (median age 71 years, range 65 – 92 years) who received aQIV and rZV concomitantly, 8 out of 122 (6.2%) reported at least one severe solicited local reaction and 7 out of 123 (5.4%) reported at least one severe solicited systemic reaction. The findings were consistent with coadministration of non-adjuvanted standard dose QIV and rZV and supported coadministration of aQIV and rZV among older adults.[39]

Likewise, coadministration of aQIV with $AS01_E$-adjuvanted respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVpreF, Arexvy®, GSK) was well tolerated and the safety profile was clinically acceptable.[40] The adjuvant in the RSVpreF vaccine is the same as that used in rZV but at half the dose. During a phase 3 RCT in Europe, solicited systemic adverse events were reported more frequently after coadministration than sequential administration, but no increase in severity or duration was seen. The rates of all adverse events were balanced between the groups. Among 1,045 participants aged 65 years and over (mean age 72 years), no cases of Guillain-Barré syndrome were reported although one case of giant cell arteritis was potentially vaccine-related.[40]

A systematic review of coadministration with seasonal influenza vaccines and COVID-19 vaccines found no safety concerns, regardless of the types of influenza or COVID-19 vaccines given.[41] No safety alerts were released following implementation of influenza and COVID-19 vaccines coadministration during 2021 – 2022 in any country.[41]

Special groups

No safety concerns were identified around the use of aTIV in immunocompromised adults aged from 18 years (including those living with HIV, and recipients of haematopoietic stem cell transplant or solid organ transplant), or in institutionalised older adults and adults receiving regular medical care. Local reactions were more common in those receiving regular medical care following aTIV than those who received standard TIV. Shivers and fever occurred more commonly in those living with HIV.[37]

Summary

As would be expected when enhancing the immune response, adjuvanted influenza vaccine is slightly more reactogenic than standard influenza vaccine. MF59® adjuvant has been added to seasonal influenza vaccine for almost two decades and consequently, this vaccine has a well-defined safety profile. No safety concerns have been raised in older adults, in whom, adverse events are generally mild to moderate in severity and of a short duration. No significant increase in adverse events was show when aTIV was administered to adults with immunocompromise or multiple comorbidities.

Coadministration of adjuvanted influenza vaccine with saponin-based adjuvant (AS01) containing vaccines does not appear to have a significant additive effect, and reactogenicity profile is in line with that of the AS01-containing vaccines. No literature was found giving more than two reactogenic vaccines at one time.

Immunogenicity

Typically, the immunogenicity of influenza vaccines is measured by neutralising antibody responses against haemagglutinin (by haemagglutinin inhibition assay, HAI) and although HAI titres of ≥1:40 are considered seroprotective, antibody levels are not commonly linked directly with clinically relevant outcomes. Few studies have assessed the T cell response and memory induced by influenza vaccines, which may have importance in the function of adjuvants. The focus of this review is on the use of adjuvanted influenza vaccine in older adults, however where comparisons are relevant, the immune responses in children and younger adults are given. See Table 9 for details of studies reviewed.

Comparison between adjuvanted and non-adjuvanted influenza vaccines

Superiority of adjuvanted IIV over standard IIV was not supported in older people by a meta-analysis conducted by Beyer et al (2020).[42] The systematic review and meta-analysis, which compared squalene-adjuvanted and non-adjuvanted (aqueous) seasonal influenza vaccine, consisted of 49 RCTs published between 1999 and 2017 across all age groups (predominantly young children and older adults, although one study included adolescents). In most cases, non-inferiority was demonstrated, regardless of age. This meta-analysis found the additional benefit of adjuvant in influenza vaccines over standard influenza vaccine was greatest in young children and decreased with increasing age. Superiority was noted predominantly in children (i.e. in 90% of comparisons in young children compared with only 9% in older adults). The extent of the adjuvant effect appeared to be associated with preseason immunity, which was lowest in young children.[42]

Beyer et al (2022) conducted a subsequent review of three meta-analyses and one clinical trial.[43] Analysis of HAI geometric mean titre ratios (GMTR) showed an adjuvant effect with GMTR of 1.5 (at 95% CI). But the studies were inconsistent as to whether effect sizes of under 1.5 were considered clinically relevant, and whether below this level, adjuvanted IIV could be considered superior to standard IIV. It was proposed that a threshold of GMTR of 1.5 would be equivalent to a seroresponse rate difference of 5%. A small uptick in GMTR was seen in immunosenescent older adults when compared to younger adults, but the increase was more marked in elderly mice. It was suggested that adjuvant may play a broader role in immunity than is measured by differences in serum antibody levels alone. Evidence indicated clearly that any annual influenza vaccination was better than none, irrespective of the type of vaccine.[43]

A meta-analysis of early-phase clinical trials during 1992 – 2013 (conducted by Seqirus and Novartis) found adjuvanted TIV elicited statistically higher anti-HA antibody responses than standard TIV in older adults, in the breadth and duration of the immune response for all the vaccine influenza virus strains tested, including for A/H3N2. The GMTR was considered non-inferior when the lower 95% CI was over 0.67 and superiority was statistically significant if over 1 (i.e. less than 1.5 used in the meta-analyses described above).[44]

Comparison between adjuvanted and high-dose influenza vaccines

A comparison was made between the humoral response immunogenicity of adjuvanted and high-dose influenza vaccine when given to adults aged 65 – 100 years living in long-term care facilities.[45] Data from a phase 4 active controlled trial in the US, found that both vaccines induced a strong humoral response. When the HAI titre seroconversion rates were compared, the data favoured the hd-TIV, although both vaccines induce seroprotection (HAI titre ≥1:40) against all strains in over 80% of participants. When anti-neuraminidase antibody was compared, the data favours aTIV. These data suggested a potential role for an anti-neuraminidase response in protection against influenza,

complementing rather than being dependent on the haemagglutinin response.[45] The findings support preferential recommendations for either of these enhanced vaccines in older adults.

All enhanced influenza vaccines (aIIV, hd-IIV and RIV) were shown to have improved immunogenicity over standard QIV in a study conducted in community-dwelling older adults aged 65 – 82 years in Hong Kong.[46] The greatest differences were seen for HAI titres against A/H1N1 and A/H3N2, but not influenza B, and for a recombinant influenza vaccine. The largest difference was seen for A/H1N1, with greater than four-fold rise in HAI titres of ≥1:40 in 60% (95% CI 43 – 67%) of participants who received aQIV and 59% (52 – 66%) for hd-TIV compared with 42% (95% CI 30 – 50) of standard QIV recipients.[46] The mean fold rise in microneutralisation assay titres were 2.9-fold for aQIV, 3.4-fold for hd-QIV and 2.3-fold for QIV. Enhanced vaccines, but not standard vaccine, were also associated with a boost in IFN-γ $CD8^+$ T cells against B/Victoria. The study was unable to extrapolate immunogenicity to clinical effectiveness.[46]

Coadministration with other vaccines

No clinically relevant interference was shown when adjuvanted influenza vaccine was given concurrently or sequentially with either an adjuvanted RSV vaccine (Arexvy) or mRNA-Covid vaccine (Comirnaty).[40, 41]

Special groups

A meta-analysis (Chen et al 2020) found that in general adjuvanted influenza vaccine could improve influenza vaccine immunogenicity in patients living with HIV infection, in terms of GMT, seroconversion and seroprotection rates. However, studies lacked comparisons between healthy and HIV-infected groups.[47]

Adjuvanted and high-dose influenza vaccines improved humoral immunity against influenza in recipients of solid organ transplants during a STOP-FLU clinical trial conducted in Switzerland and Spain. Seroprotective response rates at day 28 were 42% for TIV, 60% for aTIV and 66% for hd-TIV. The risk differences for both aTIV and hd-TIV were significant compared with standard TIV ($p<0.001$) but not statistically different from each other ($p=0.085$).[48]

Cell-based adjuvanted influenza vaccine

A proof-of-concept study suggested that adding adjuvant to cell-based QIV enhances the immune response against haemagglutinin and neuraminidase for all four influenza strains in 449 older adults (mean age 65 years, range 50 – 87 years). When comparing GMTRs from HAI assays using cell-based strains, adjuvanted QIVc had a lower haemagglutinin antibody response to influenza A strains than hd-QIV, and a higher response to influenza B. Compared with egg-based aQIV, the cell-based aQIV had a higher response to cell-grown influenza strains used in the HAI assay. However, adding adjuvant to cell-based influenza vaccine did not enhance the persistence or breadth of the antibody response against heterologous influenza strains.[49]

Summary

The addition of adjuvant to standard influenza vaccines modestly improved the antibody response in older adults (GMTR >1 – 1.5) and in those with immunocompromise. Some data suggest that adjuvant may play a broader role in immunity than is observed with differences in the serum antibody levels and HAI assay titres. For example, adjuvant appears to enhance the neuraminidase response. Coadministration with other vaccines does not result in clinically relevant interference of either vaccine. Adding adjuvant to cell-based IIV appears to have a similar effect as it does in egg-

based IIV, which might be advantageous in years where there is an egg-adaptation mismatch that reduces vaccine effectiveness in older adults.

Efficacy and effectiveness

Much of the recent literature on effectiveness was in the form of systematic reviews and meta-analyses, often conducted by or funded by Seqirus (manufacturer of Fluad Quad®). These systematic reviews frequently include the same clinical trials and retrospective cohort studies conducted over the same influenza seasons. No head-to-head randomised clinical trials have directly compared adjuvanted and non-adjuvanted (standard dose) influenza vaccines

Some studies did not use laboratory-confirmed influenza as an endpoint, rather using influenza-related medical encounters, without PCR-testing. Efficacy outcomes also depended on the definition of influenza-like illness used in the studies.

Greater efficacy against more clinically significant influenza-like illness was shown with aQIV during a season when the vaccine strains did not match the circulating strains. In a Seqirus-funded phase 3 RCT, using Tdap as the control vaccine, efficacy of aQIV was 19.8% (95% CI -5.3 to 38.9) against all PCR-confirmed influenza. The majority (85%) of isolates were A/H3N2 that mismatched the vaccine strain. Efficacy against antigenically matched strains was 49.9% (-24.0 to 79.8). When efficacy was reassessed in a post hoc analysis, using the WHO influenza-like illness (ILI) definition instead of the predefined protocol criterion, efficacy against more clinically significant disease improved. Vaccine efficacy against the protocol ILI (respiratory and systemic symptoms, not necessarily including fever) was 19.8% (-5.3 to 38.9) compared with the VE of 51.1% (28.2 – 66.7%) against the WHO ILI definition (fever ≥38°C and cough).[50]

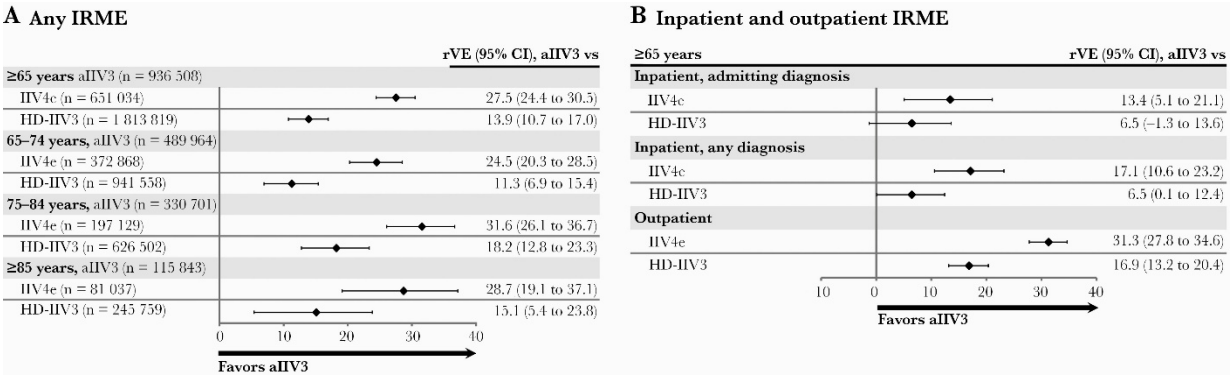
Relative effectiveness compared with standard influenza vaccine

A systematic review (Gärtner et al 2022, funded by Seqirus) conducted 11 analyses from nine real-world evidence studies that involved 53 million participants aged ≥65 years during influenza seasons from 2006 – 2009 and 2011 – 2020. It showed that adjuvanted (aTIV) and high-dose (hd-TIV) influenza vaccines are both effective for vaccination programmes in older adults and are preferred over standard-dose (TIV or QIV) influenza vaccines. The relative effective of aTIV vs TIV and QIV ranged from 7.5% – 25.6% and 7.1% – 36.3%. The risk of bias in these studies were moderate to high with no head-to-head RCT included.[51]

Another Seqirus systematic review (Coleman et al 2021), with many studies conducted over the 2017/18 season, found aTIV to be more effective than standard QIV at preventing laboratory-confirmed influenza and influenza related medical encounters; although comparisons with TIV tended to be earlier.[52]

A US-based study conducted by Seqirus found that aTIV was more effective than QIV or hd-TIV (see below) at preventing influenza-related medical encounters (IRME) in adults aged ≥65 years during the 2019/2020 influenza season (see Figure 4). The retrospective cohort study of the 2019/2020 influenza season used electronic health records and linked medical claims data in the US to assess the effectiveness of adjuvanted TIV, standard QIV and high-dose TIV in adults aged 65 years and over (mean age 75 years ± 7 years).[53] The population consisted of over 3.5 million individuals, of whom 26% received aTIV, 18.3% received QIV (plus 4.3% TIV) and 51% received hd-TIV.

Figure 4: Relative vaccine effectiveness of adjuvanted IIV compared with standard QIV and high-dose TIV in adults aged ≥65 years in the US (2019/2020 season). A) Any influenza-related medical encounter; B) inpatient and outpatient influenza-related medical encounters (Imran, 2022, open access)



Abbreviations: IRME – influenza-related medical encounters; aIIV3 – trivalent adjuvanted inactivated influenza vaccine; IIV4c – quadrivalent cell-based influenza vaccine; IIV4e – egg-based influenza vaccine; HD-IIV3 – trivalent high-dose influenza vaccine; rVE – relative effectiveness

Older adults with underlying health conditions

The effectiveness of aTIV was examined in a proportion of the above US cohort (approx. 1.67 million older adults) with at least one underlying condition associated with increased influenza risk.[54] The top three comorbidities were heart disease, metabolic disorders and endocrine disorders. Adjuvanted TIV was found to be more effective than standard QIV in this cohort against IRME, outpatient IRME and influenza or pneumonia-related hospitalisation. During this season, both vaccines had reduced effectiveness against A/H1N1pdm09 and B/Victoria due to antigenic drift in the circulating virus (absolute VE of around 30%).[54]

A further analysis in 4.3 million of the above cohort investigated the relative effectiveness of aTIV against cardiorespiratory hospital diagnosis (including respiratory infections, myocardial infarction and ischaemic stroke).[55] It found that there were fewer cardiorespiratory hospitalisations (for all virus infections, influenza and pneumonia, and myocardial infarction) in older adults who were vaccinated with aTIV than those vaccinated with QIV (rVE 9.0%; 95% CI 7.7 – 10.4%). Fewer hospitalisations for ischaemic stroke were also shown for those vaccinated with aTIV compared with QIV. The relative effectiveness of aTIV to QIV was shown as 25.3% (17.7 – 32.2%) against influenza hospitalisation in this cohort.[55]

In Canada, both TIV and aTIV were found to be effective against influenza-related hospitalisation in older adults (VE ranged from 45% – 54%) over three seasons, with no statistically significant difference overall between the vaccines by sex, age or influenza season. Before adjusting for frailty, adjuvanted vaccine had higher effectiveness than non-adjuvanted TIV against A/H1N1pdm09 but lower against A/H3N2. When frailty was considered, vaccine effectiveness remained the same for TIV but increased for aTIV. Findings indicated aTIV was around 25% (OR 0.75, 0.61 – 0.92) more effective than TIV against laboratory-confirmed influenza in frail elderly adults, mostly against A/H1N1. With a small sample size, aTIV also appeared more effective than TIV in adults aged ≥85 years. A test-negative designed study used data pooled from Serious Outcomes Surveillance of the Canadian Immunisation Research Network to assess the effectiveness of adjuvanted and non-adjuvanted influenza vaccines against influenza-associated hospitalisation of older adults over three seasons from 2012 to 2015.[56] Included were 3,441 influenza cases and 3,660 controls aged ≥65

years. The majority (85.6%) received standard influenza vaccine (TIV) and 526 had received adjuvanted TIV (aTIV). Of the frailest adults, 33.3% received aTIV and 5.6% received TIV and of the non-frail adults 55.4% received TIV and 15.2% received aTIV.[56]

Comparison with high-dose influenza vaccine

Adjuvanted and high dose vaccines appeared to have similar effectiveness against influenza in older adults.[57] A systematic review (Domnich, 2022) that compared the effectiveness of adjuvanted and high-dose influenza vaccines found that no preference could be drawn to recommend one over the other. It reported no head-to-head RCT studies as most studies were retrospective cohort studies in US older adults. None of these studies had laboratory-confirmed influenza as an endpoint and had a moderate risk of bias. Pooled estimates of relative effectiveness were close to null.[57]

As mentioned above, US-based cohort study found that aTIV was more effective than hd-TIV at preventing influenza-related medical encounters (IRME) in adults aged ≥65 years during the 2019/2020 influenza season.[53] Of the population of over 3.5 million individuals, 26% received aTIV and 51% received hd-TIV. However, when influenza was the admitting diagnosis for inpatients, the relative vaccine effectiveness between aTIV and hd-TIV was not statistically different.

A further analysis in 4.3 million of the above cohort investigated the relative effectiveness of aTIV against cardiorespiratory hospital diagnosis (including respiratory infections, myocardial infarction and ischaemic stroke). It found that there were fewer cardiorespiratory hospitalisations (for all virus infections, influenza and pneumonia, and myocardial infarction) in older adults who were vaccinated with aTIV than those vaccinated with hd-TIV (rVE 3.9%; 95% CI 2.7 – 5.0%). Effectiveness against influenza hospitalisation was 9.7% (1.0 – 17.0%) higher for adjuvanted TIV in this cohort relative to hd-TIV.[55]

In Denmark, funded aQIV significantly improved influenza protection for older adults during the 2024/2025 season, compared with standard QIV.[58] During this influenza season Danish adults aged ≥70 years were offered funded aQIV, those aged ≥65 years were offered standard QIV and a subgroup were randomised to receive either hd-QIV or standard QIV.[58] Among 20,615 people aged ≥65 years, 74% received aQIV, 20% received standard and 7% receive hd-QIV. The guideline in Denmark is to swab anyone belonging to a risk group to test for influenza A and B, including those aged ≥65 years, who present with an influenza-like illness (ILI) to general practice or those presenting to hospital with ILI and lower respiratory tract symptoms. Overall, for hospitalised and non-hospitalised cases, vaccine effectiveness of aQIV (48%, 95% CI 42 – 52%; p<0.0001) was significantly greater than standard QIV (33%, 24 – 41%); hd-QIV had a similar effectiveness to aQIV (50%; 38 – 59%). Likewise for hospitalised influenza cases, aQIV was significantly more effective than standard QIV (47% vs 26%; p=0.001).[58] It was concluded the benefits of influenza vaccination against severe influenza outcomes were enhanced with aQIV or hd-QIV in older adults.[58]

Effectiveness was comparable between aTIV and hd-TIV against test-confirmed influenza in hospital ED visits or admission in older adults aged ≥65 years.[59] Pooled data over three influenza seasons (2017 – 2000) from retrospective test-negative designed studies in the US were analysed to investigate the relative effectiveness of aTIV in comparison to hd-TIV.

Summary

The benefits of influenza vaccination in older people can be enhanced by adjuvanted influenza vaccine. The magnitude of the improvement in effectiveness is dependent on the vaccine, age and health status of the recipients, and the circulating virus strains. Effectiveness appears to be greatest

in older adults with comorbidities and those with a high degree of frailty. However, the stated efficacy gains in the clinical studies vary on the criteria used to determine non-inferiority. Adjuvanted influenza vaccine provides further protection against cardiorespiratory conditions, such as myocardial infarction and ischaemic stroke, as well as respiratory infections.

Influenza vaccination, with any of the available vaccines is beneficial. Either adjuvanted or high-dose influenza vaccines provide some additional benefit over standard influenza vaccines, particularly in those at highest risk of more severe outcomes.

High-dose inactivated influenza vaccine

High-dose inactivated influenza vaccine (Fluzone High-Dose, Sanofi-Aventis) contains more haemagglutinin than the standard dose counterparts (60µg per vaccine strain compared with 15µg). High-dose influenza vaccines (hd-TIV or hd-QIV) are not currently available nor approved for use in New Zealand but are in use in Australia for the 2025 influenza season for adults aged 60 years and over.

Some of the studies into high-dose IIV are presented above when compared with adjuvanted vaccine. Presented here are further studies of comparing high-dose with standard-dose IIV or no vaccination. See Table 10 for further details of the studies presented below.

Safety

Generally, high-dose influenza vaccine is well tolerated but with potentially more reactogenicity than standard IIV, particularly at the injection site, as might be expected with the four-times higher dose of antigen.

During a phase 3 clinical trial conducted in Europe, comparing hd-QIV with standard dose QIV, the most frequently reported reaction was injection-site pain.[60] As seen with other vaccines, the rate of injection-site pain was higher in those aged 60 – 64 years than those aged over 65 years (52% vs 39%), and higher than QIV (24% vs 18%, respectively). The most frequently reported systemic reactions were myalgia (31% hd-QIV) and headache (30% hd-QIV vs 20% QIV), with some participants reporting malaise and shivering. No serious adverse event was considered vaccine-related and no adverse event of special interest occurred within 28 days of vaccination.[60]

A Vaccine Safety Datalink study in the US found no statistically significant signal for Guillain-Barré Syndrome (GBS) within 42 days of vaccination with hd-TIV in adults aged 65 years and over (median aged 73 years, IQR 69 – 79 years). The analysis of almost 650,000 vaccinations with hd-TIV was conducted following the 2018/2019 US influenza season.[61]

Coadministration with other vaccines

No significant differences in safety profiles were seen between groups of older adults who received either hd-QIV or aQIV when coadministered administered with $AS01_B$-adjuvanted recombinant zoster vaccine (rZV, Shingrix® GSK) during an RCT in the US.[39] In the group of 137 community-dwelling participants aged over 65 years (median age 71 years, range 65 – 92) who received hd-QIV and rZV concomitantly, 6/130 (4.4%) reported at least one severe solicited local reaction; and 13/123 (9.6%) reported at least one severe solicited systemic reaction with the first dose of rZV. A

higher proportion of participants reported severe reactions within 1 – 8 days post-vaccination when hd-QIV was administered with the second rZV dose (non-inferiority with aQIV, p=0.001). The study supported coadministration of aQIV or hd-QIV with rZV among older adults. The findings were consistent with the prelicensure studies of each vaccine and consistent with coadministration of rZV with non-adjuvanted, standard dose QIV.[39]

Summary

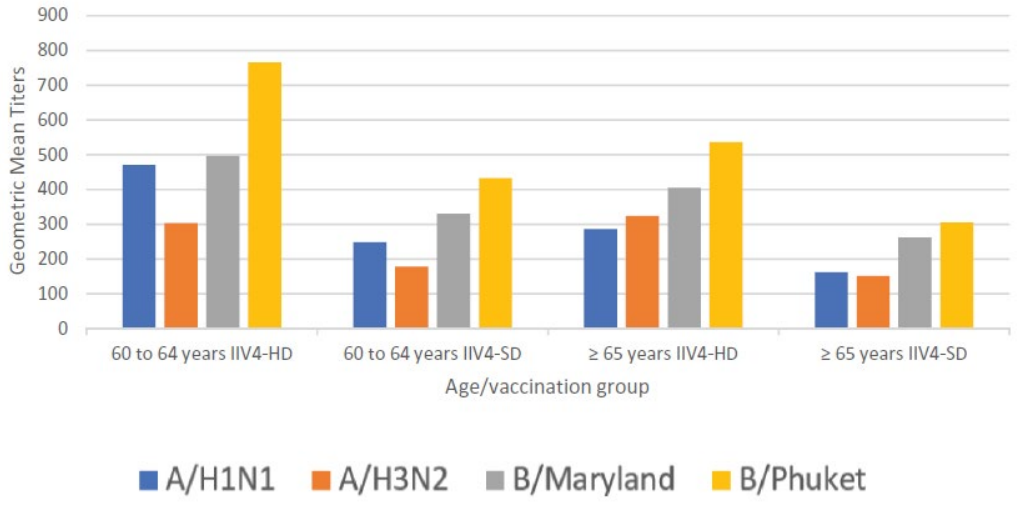
High-dose influenza vaccines are slightly more reactogenic than standard dose vaccines, with a higher proportion of recipients reporting mild to moderate injection site pain, myalgia and headaches. No serious adverse events have been associated with this vaccine. Coadministration did not increase the risk for adverse events. No increase in risk of GBS has been detected.

Immunogenicity

A systematic review of seven clinical trials (published up to 2017) was conducted by the WHO and CDC comparing high and standard dose influenza vaccines in adults aged 60 years and over.[62] It found that hd-IIV induced 82% (73 – 91%) significantly higher post vaccination HAI titres against A/H3N2 than standard dose vaccines. The geometric mean titres (GMT) were significantly higher than those induced by adjuvanted and intradermal IIV against A/H1N1 and B/Victoria, but all of the enhanced vaccines induced higher antibody levels than standard vaccine.[62] The authors reported that head-to-head studies conducted over multiple seasons would be informative.

A phase 3 RCT conducted in Europe compared hd-QIV with standard dose QIV in 1,528 older adults (mean age 67 years, range 60 – 93 years) during the 2019/20 season. Hd-QIV had greater immunogenicity for all four virus strains compared with QIV. More participants who received hd-QIV achieved seroprotection (HAI titres ≥1:40) than in the QIV groups, and slightly higher GMTR were shown in the younger group. When serum neutralising antibodies were compared the younger age group had the highest titres and lowest were against A/H3N2. But in any group, 99% – 100% of the participants achieved seroprotective antibody levels (titres of ≥1:10; see Figure 5).[60] The immune response against hd-QIV was robust irrespective of prior influenza vaccine history or the presence of underlying medical conditions associated with increased risk for influenza complications.

Figure 5: Summary of neutralising antibody titres at base line and day 28 post vaccination with high dose (IIV4-HD) or standard dose QIV (IIV4-SD) (Pepin 2021, open access)



Special groups

High-dose influenza vaccine improved humoral immunity against influenza in solid organ transplant recipients during STOP-FLU clinical trial conducted in Switzerland and Spain. Seroprotective response rates (with at least four-fold increase in HAI titres) at day 28 were 42% for TIV and 66% for hd-TIV recipients. The difference in vaccine response rates (i.e. proportion of patients with seroconversion for at least one viral strain) for hd-TIV was statistically significant compared with standard TIV ($p < 0.001$), but not statistically different from aTIV ($p = 0.085$).[48]

An US-based phase 4 RCT assessed hd-TIV use in 40 patients aged 18 – 64 years with inflammatory bowel disease being treated with either anti-TNF monotherapy or with vedolizumab, which specifically targeting gut inflammation.[63] Hd-TIV induced higher anti-A/H3N2 antibody concentrations than standard TIV in patients who received anti-TNF therapies and controls, but there was no difference between hd-TIV and TIV against A/H1N1 or B/Victoria. The antibody levels in those who received hd-TIV had waned faster than the TIV dose, such that there was no difference between the groups after 6 months. Patients who received vedolizumab had comparable response to TIV as healthy controls.[63]

In a phase 2 RCT in the US, two doses of hd-TIV given at least 4 weeks apart was more immunogenic against A/H3N2 (GMTR 2.09; 95% CI 1.19 – 3.68) and B/Victoria (GMTR 1.61; 1.00 – 2.58) than standard TIV in patients 3 – 23 months post allogenic haematopoietic stem cell transplantation (HSCT). Higher GMTs were seen at 1 month and 6 months after dose 2. At 6 months post vaccination, the GMTRs between high and standard dose TIV were similar to those seen after dose 1.[64] Revaccination of individuals following HSCT routinely requires two doses given 4 weeks apart in the first season post-transplant. This review has not considered the use of two doses of influenza vaccine in one season in any other immunocompromised groups.

A prospective pilot study at the Mayo Clinic, US, showed that high-dose TIV was able to induce influenza seroprotection in patients with monoclonal B cell lymphocytosis (MBL) and untreated chronic lymphocytic leukaemia (CLL) even though the responses were suboptimal.[65] Patients with MBL responded better than those with CLL, as would be expected with less advanced immunocompromise (i.e. with high baseline total immunoglobulin and lymphocyte counts).[65]

Summary

High-dose influenza vaccine induces a greater humoral response than standard dose vaccine in older adults and those with immunocompromising medical conditions. The difference is particularly marked against A/H3N2. Hd-IIV could be considered for people with severe immunocompromise (such as lymphocytosis or leukaemia) to provide the best opportunity to reduce the risk of severe influenza complications.

Efficacy and effectiveness

The following gives a summary of the most recent studies and systematic reviews for high-dose inactivated influenza vaccines. For comparisons between high-dose and adjuvanted influenza vaccine, see *Comparison with high-dose influenza vaccine*. For further details of the studies, see Table 10.

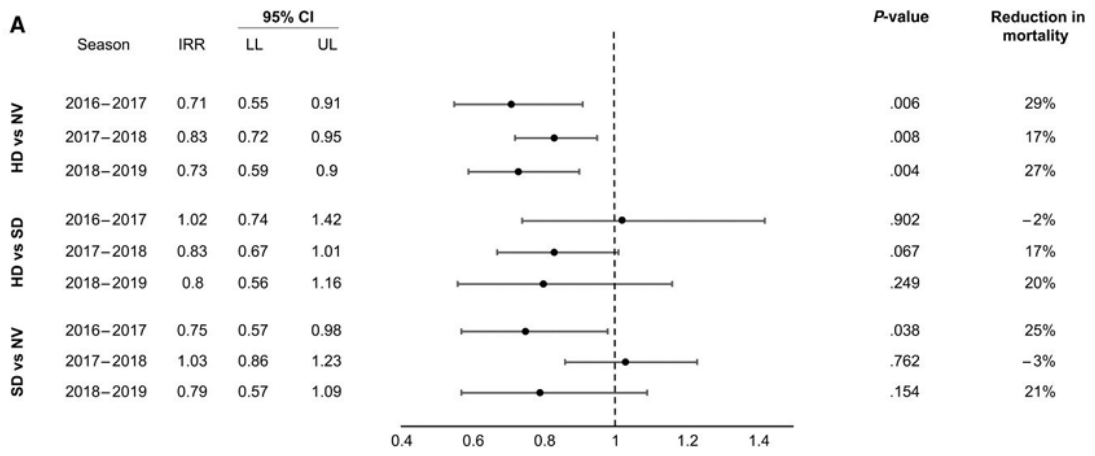
A systematic review conducted by the European Centre for Disease Control (Comber, 2023) found that there were limited studies on hd-IIV efficacy. The data were from largely cohort studies (nine

studies) with a range of outcomes and two RCT comparing hd-IIV with standard dose. The evidence suggested that hd-IIV improved protection against influenza and associated complications compared with standard dose and no vaccination in older adults. A meta-analysis of the cohort studies showed a fixed effect rVE of 13.5% (7.3 – 19.3%) against influenza-related hospitalisation.[66]

The effectiveness of hd-TIV was assessed over 10 consecutive influenza seasons with vaccine matched and mismatched circulating virus. Sanofi conducted a systematic review and meta-analysis (Lee et al, 2021) that compared hd-TIV effectiveness with standard TIV in over 22 million people.[67] It showed Hd-TIV to be consistently more effective than standard TIV in adults aged ≥65 years in reducing influenza cases and influenza-associated complications, irrespective of the circulating strain and antigenic match. Notably, the relative effectiveness of hd-TIV to standard TIV against influenza-related hospital admission was 12% (7 – 16%) and 40% (19 – 56%) against mortality due to pneumonia and influenza. Similar improvements in effectiveness were shown for both matched and mismatched seasons and in seasons where either A/H3N2 or A/H1N1 predominated.[67]

Sanofi also assessed the benefits of hd-TIV against mortality following influenza-related hospitalisation in comparison to no vaccine.[68] A retrospective cohort study of US medical claims data during influenza seasons from 2016 to 2019 identified 44,456 influenza cases aged ≥65 years. Of these, 52% were unvaccinated, 33.8% had received hd-TIV and 14.2% received standard TIV. As shown in Figure 6, when compared with no vaccine, hd-TIV reduced mortality by 17 – 29%. In the 2016/2017 season, with a good match between the vaccine and circulating virus (with 74% of tested cases were A/H3N2), similar protection was provided by hd-TIV and standard vaccine. In this year, standard vaccine reduced mortality by 25% (IRR 0.75, 95% CI 0.57-0.98) compared with no vaccine. During two mismatched seasons, hd-TIV reduced mortality by 17% – 20% compared with standard vaccine, although without statistical significance. The findings concluded that high-dose influenza vaccine significantly reduces the risk of mortality following influenza-related hospitalisation compared with those who are unvaccinated. In a season, where vaccines matched circulating strain, comparable protection was provided by standard vaccine. In a season where there was a mismatch, high-dose vaccine was more protective and reduced mortality among breakthrough infections than standard dose. [68]

Figure 6: Forest plot comparing high dose (HD), standard dose (SD) and no influenza vaccine (NV) against the relative risk and percentage reduction in mortality for each influenza season (after entropy balancing for each comparison cohort).(Chaves et al 2023, open access)



Distribution of influenza viruses by season:
2016/17 – 74% A/H3N2 (well-matched), 23% B, 3% A/H1N1;

2017/18 – 60% A/H3N2 (poorly matched), 29% B, 11% A/H1N1;
2018/19 – two waves, 52% A/H1N1 then 42% A/H3N2 (mismatched), 6% B.

Two further open-label, randomised clinical trials were conducted by Sanofi to investigate the efficacy of hd-IIV against severe outcomes in older adults compared with standard vaccine: the DANFLU study was conducted in Denmark with over 332,000 participants over three influenza seasons from 2022 – 2025; and the second in Galicia, Spain (GALFLU) with over 103,000 participants over two seasons 2023 – 2025.[69, 70] Against the primary endpoint of hospitalisation for influenza or pneumonia, DANFLU did not find that hd-IIV was significantly more effective than standard dose vaccine. However, when the incidence of influenza ICD-10 coding or laboratory-confirmed influenza was assessed, hd-IIV was 44% and 36% more effective at preventing influenza hospitalisation than standard dose, respectively. Relative effectiveness of hd-IIV was also higher in individuals with at least one comorbidity.[69] In the GALFLU study, among community-dwelling older adults, those who received high-dose vaccine were 24% less likely to be hospitalised with influenza or pneumonia (including almost 20% less laboratory-confirmed influenza) than those who received standard dose influenza vaccine. In this study, high-dose IIV was favoured against all the secondary endpoints.[70]

Summary

Evidence suggests that high-dose influenza vaccine helps to lower the severity of influenza and complications associated with hospitalisation and death in older adults. It provides some additional benefit over standard dose vaccine, even in years when there is a degree of mismatch between the circulating and vaccine A/H3N2 viruses. The relative effectiveness of either adjuvanted or high-dose influenza vaccines are similar when compared with standard vaccine.

Recombinant influenza vaccine

Recombinant influenza vaccine (RIV) contains pure haemagglutinin that is produced using a baculovirus vector system in insect cells (FluBlok® or Supemteck®, Sanofi). During manufacture of traditional inactivated influenza vaccines, through viral replication and purification, complex glycosylation of the HA protein prevents access to some of the antigenic sites. Recombinant haemagglutinin undergoes less complex glycosylation, exposing more antigenic sites and the potential for cross-protection, even when there is a mismatch between circulating virus and predicted vaccine virus. This vaccine contains 45µg haemagglutinin per virus strain (compared with 15µg for standard-dose inactivated vaccine and 60µg in high-dose inactivated vaccine). Unlike inactivated influenza vaccines, RIV contains no other antigens, such as neuraminidase, which may play supportive roles in the immune response or immune memory against influenza virus.

For details of the following studies see Table 11.

Safety

Despite having higher antigen content, the safety profile of RIV was like that of standard IIV in healthy adults aged 18 – 49 years. An RCT found it to be safe and well tolerated with reports of local and systemic reactions at similar frequency and severity to QIV within 7 days of vaccination.[71] Around half of the vaccine recipients reported mild injection-site pain and tenderness. Erythema was around four times more frequent in those who received RIV4 than QIV (4.2% vs 0.9%). [71]

A systematic review by O Murch et al (2023) reported a potentially higher incidence of chills across ten RCTs in those who received RIV (risk ratio 1.33, 95% CI 1.03-1.72) but found no other differences in adverse events when compared with standard dose IIV.[72]

Special groups

There is limited data for the use of RIV in special groups. The O Murchu (2023) systematic review found one study in which six out of 27 patients with non-Hodgkin lymphoma reported injection site pain, malaise and myalgia after RIV.[72]

A post-licensure observational cohort study of 15,574 Californian adults with Chinese ethnicity found no safety concerns regarding giving RIV, with and without comorbidities, within the Kaiser Permanente Northern California (KPNC) members. These were compared with 27,110 adults of Chinese ethnicity who received QIV.[73] No statistically significant difference was shown in medically attended adverse events of special interest (AESI) within a 41-day risk interval between those who received RIV and QIV.

As part of the same KPNC cohort study, the safety of RIV was assessed in pregnancy. It found no statistical difference for any pregnancy, birth or neonatal/infant outcomes between those who received RIV4 or QIV during pregnancy.[74] The subset included 48,781 pregnant people and 47,384 live births during the 2018/19 and 2019/20 influenza seasons in Northern California.

Conclusion

Despite having a higher dose of haemagglutinin than standard influenza vaccines, the safety of RIV is comparable. Erythema and chills are reported frequently with RIV than IIV. No safety concerns have arisen to date, including when giving in pregnancy. Data is limited around the safety in older adults or immunocompromised groups.

Immunogenicity

The immune response to recombinant influenza vaccine is likely to differ from that of standard IIVs for three reasons:

1. the antigen (haemagglutinin) content is three times higher (45µg per strain vs 15µg)
2. it contains only pure haemagglutinin
3. due to less glycosylation more antigen sites may be accessible to the immune system.

As mentioned before, one limitation of immunogenicity studies of influenza vaccines is which strains are used in the assays and the vaccine of interest. In the case of RIV, the antigen is not affected by the medium in which the virus is grown because it does not rely on propagation of virus in cells or eggs, but the assays used to assess immunogenicity use virus strains grown in either medium. In this way, the assay results may differ from the actual immunity of vaccinated people when exposed to the circulating strains and therefore cannot be fully extrapolated to clinical efficacy.

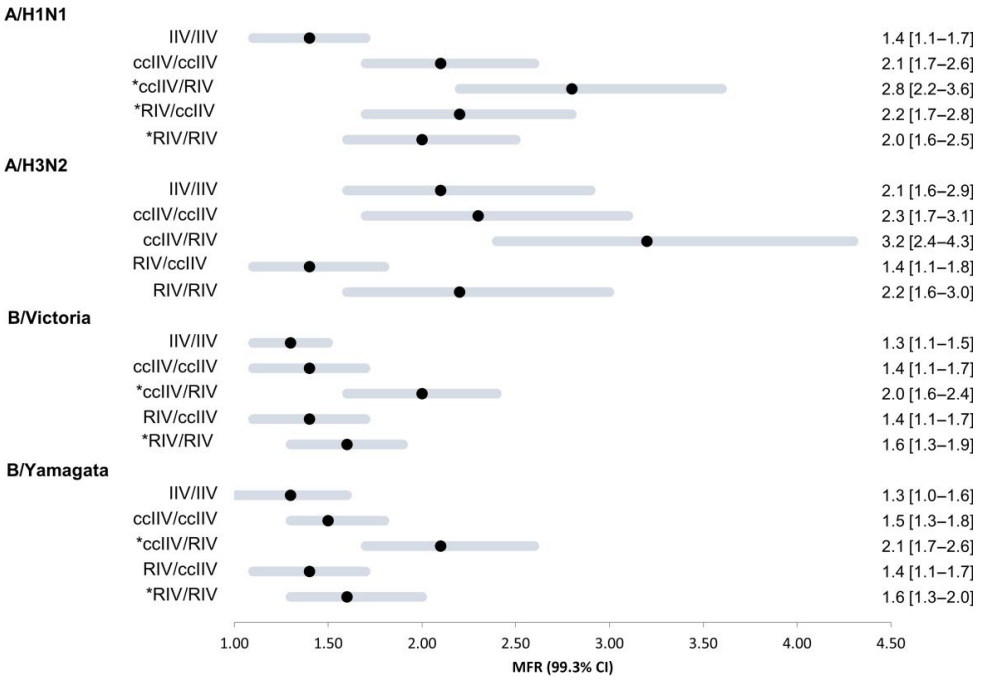
Antibody titres induced by RIV are comparable or higher than by cell-based or egg-based QIV in adults aged under 64 years.[75-77] CD4+ T cell cytokine responses at day 14 post vaccination were shown to be greater for all HA types than TIVc and TIV in adults aged 18-49 years over three seasons. Although higher antigen content could be a factor, RIV performed better than hd-TIV.[78]

In healthcare workers in the US, who were vaccinated in the previous season with QIVc, QIVe or RIV, RIV elicited higher antibody titres compared with those who received QIVc or QIVe over two seasons (QIV/QIV reference group).[77] It was unclear whether this was due to the higher antigen dose or

differences in responses to the recombinant HA. Whether received previously in the preceding season or only in the current season, RIV induced robust antibody responses against all vaccine components. The exception was for A/H3N2 in the group who received RIV then QIVc. (See Figure 7)[77]

Figure 7: Forest plot of mean fold rise (MFR) geometric mean haemagglutinin inhibition antibody titres at 1 month post-vaccination by two-season vaccine combination, in comparison to standard egg-based vaccine in both seasons (Gaglini et al, 2023, open access)

IIV – egg-based inactivated influenza vaccine (QIV); ccIIV – cell-based QIV; RIV recombinant influenza vaccine (RIV4). * - p<0.007; MFR - geometric mean of the ratio of post-vaccination and pre-vaccination titre for each participant.



A similar study conducted in Israel also showed that RIV4 had improved immunogenicity against influenza vaccine virus strains over QIV among healthcare workers who were frequently and infrequently vaccinated against influenza.[76]

A comparison of the immune response against A/H3N2 in healthy adults found that antigen match and vaccine dose are both important to elicit optimal antibody responses against contemporary wild-type A/H3N2 viruses.[79] RIV induced 3.9- to 4.3-fold significantly higher neutralising antibody titres than TIVc or TIVe against two wild-type A/H3N2 strains. These findings reflected the relatively low effectiveness of TIVe and TIVc during the 2017/18 season. This difference was comparable to hd-TIV with 3.2-fold higher neutralising titre than TIVe. A greater proportion of the RIV group seroconverted to wild-type H3N2 viruses (52% and 61%) than in the hd-TIV group (38% for both viruses).[79]

One study found that both RIV and TIVc have similar immunogenicity profiles, but RIV has a preference towards epitopes on the receptor-binding domain on haemagglutinin (HA head).[80] The antibodies generate by influenza vaccines were examined using plasmablasts (antibody-secreting precursor to mature plasma cells) isolated from vaccinated healthy volunteers aged 18 – 49 years. It found that RIV induced a greater proportion of monoclonal antibodies targeting epitopes near the receptor-binding domain of the haemagglutinins than QIVc. Both induced similar frequencies of

stalk-reactive monoclonal antibodies and antibody-secreting cells. Immune imprinting in the human cohort, due to previous exposure to influenza virus, was not found to be a major bias. As in humans, in mice (naïve to influenza) the vaccines induced similar frequencies of stalk-reactive antibodies and showed that the HA-head immunodominance with RIV was independent of immune memory.[80]

Older adults

RIV4 induced particularly high antibody responses against cell-propagated A/H3N2 strains during an RCT of community-dwelling adults aged 65 – 82 years in Hong Kong.[46] RIV4 consistently induced greater responses than aQIV, hd-TIV or QIV against influenza A strains. At 30 days post vaccination, the microneutralisation assay titre mean-fold rise was 4.7-fold for RIV compared with 3.4 and 2.9-fold for hd-TIV and aQIV, and 2.3-fold for standard QIV. The proportion of participants with at least a 4-fold rise in HAI titres (≥1:40) were statistically higher for all enhanced vaccines against A/H1N1 and A/H3N2 and 60% (53 – 67%) of RIV4 recipients compared with 42% (36 – 50%) of QIV recipients. Antibody responses to B/Victoria were similar between groups (44% RIV vs 48% QIV).[46] This study could not extrapolate immunogenicity to vaccine effectiveness.

Summary

The immunogenicity of RIV is at least comparable to or greater than standard cell-based or egg-based IIV. Several factors contribute to this, namely, the antigen dose is higher; the antigen is purer and undergone fewer changes during production; and antibodies generated are targeted more towards the receptor-binding site of the haemagglutinin head. These may influence the effectiveness of the vaccine to prevent infection by providing some cross-protection with mismatched strains. Both antigen match and vaccine dose are important to elicit optimal antibody responses against A/H3N2.

Efficacy and effectiveness

Although RIV is recommended internationally and has been licenced since 2013, recent data around the efficacy and effectiveness of RIV is limited. No studies were identified that compared effectiveness of RIV against any of the other enhanced vaccines, including high-dose or cell-based QIV. Data is also limited to those aged under 65 years. For further details see Table 11.

A systematic review of literature published up to February 2020 found only two efficacy studies.[72] Although these RCT were published prior to 2019, they have been included below.

Efficacy of RIV against culture-positive CDC-defined influenza-like illness (ILI) was shown to be 45% (95% CI 18.8 – 62.6%) regardless of vaccine strain during a placebo-controlled RCT.[81] The study involved just under 5,000 adults aged 18 – 55 years (mean 32.5 years). In the 2007/08 season of this study, only eight of the 582 influenza cases were antigenically identical to the vaccine strain. Vaccine-mismatched A/H3N2 and B/Yamagata (not included in the RIV3 vaccine) were predominant. When influenza A was considered alone, vaccine efficacy increased to 54% (26.1 – 72.5%). It was unable to obtain an estimate of efficacy against vaccine-strain specific influenza. The study concluded that the findings supported the use of a pure HA vaccine in a primed population. It did not find that any minor differences in HA glycosylation and the use of a synthetic, uncleaved HA prevented an effective immune response.[81]

RIV provided 30% better protection than QIV against PCR-confirmed ILI in adults aged over 50 years. The RCT compared RIV4 with QIV in 8,604 adults aged over 50 years.[82] Based on the cumulative

incidence of PCR-confirmed ILI, effectiveness of RIV was significantly higher than QIV (hazard ratio 0.69, 0.53 – 0.9, p = 0.006). A post hoc analysis found no improvement in effectiveness against influenza B. Against influenza A (predominantly A/H3N2), RIV4 was 37% more effective than QIV (HR 0.63; 0.48 – 0.86, p = 0.003).[82]

A cluster randomised observation study in Northern California found RIV to be around 15% (95% CI 5.9 – 23.8, p = 0.002) more effective than QIV against PCR-confirmed influenza in adults aged 50 – 64 years. But no significant difference was shown for more severe, hospitalised, influenza outcomes. The population included over 1.6 million adults with 1,386 PCR-confirmed influenza cases (559 received RIV4 and 925 received QIV).[83] RIV was shown to improve protection for those with underlying conditions, such as coronary heart disease, asthma, diabetes and chronic obstructive pulmonary disease.

Conclusion

The evidence indicates that RIV is modestly (15-45%) more effective against influenza infection (particularly influenza A) than standard inactivated influenza vaccine in adults aged up to 64 years. Generally, RIV does not appear to be significantly better than standard vaccine in preventing severe influenza outcomes but could improve protection for individuals at higher risk of influenza complications with underlying comorbidities. Current data is limited, particularly due to the interruption of influenza circulation during the COVID-19 pandemic.

Live attenuated influenza vaccines

The current FluMist brand (AstraZeneca, also marketed as Fluenz®) of live attenuated influenza vaccine (LAIV) was first licensed in the US in 2003 and in Europe in 2011. It is not currently approved for use or available in the Southern Hemisphere. The UK was the first country to introduce universal vaccination of children with LAIV in 2013, starting in preschool children aged from 2 years and then expanded further as part of a school-based immunisation programme, with evidence of herd immunity to protect older adults.

In 2017, we conducted an antigen review / review of evidence on influenza, in which, details about the live attenuated influenza vaccines (LAIV) were given.[6] Another review of evidence was conducted in 2022 that evaluated the role of immunising children to control influenza in New Zealand.[12]

This review does not detail the potential role for LAIV and vaccination of children in the New Zealand influenza immunisation programme, rather it provides review of the most recent published literature on LAIV safety, immunogenicity and effectiveness. See Table 12 for details of the studies presented.

Safety

Since LAIV contains live influenza virus, it is contraindicated for individuals with severe immunocompromise, such as cellular immunodeficiencies, haematological malignancy, high-dose corticosteroids and symptomatic HIV infection. It is not contraindicated for those with asymptomatic HIV infection, receiving low dose steroids, inhaled or topical steroids or for corticosteroid replacement therapy.

In clinical trials, the most common adverse reaction was nasal congestion / rhinorrhoea. Other adverse reactions include decreased appetite, sore throat, headache, myalgia and fever. Anaphylactic reactions can occur very rarely, and this vaccine is contraindicated for those with severe egg or egg protein allergy. Due to an increased rate of wheezing reported in infants aged 6 to 23 months (5.9% within 42 days post LAIV administration vs 3.8% from injectable influenza vaccine), it is not indicated under the age of 2 years.[84]

Children with wheeze or asthma

The use of LAIV in individuals with asthma and recurrent wheeze has been evaluated by systematic reviews and other studies. Two AstraZeneca sponsored systematic reviews found no safety concerns or increases in exacerbation of asthma, wheezing or healthcare utilisation in individuals vaccinated with LAIV aged 2 to 49 years with any asthma diagnosis or recurrent wheeze.[85, 86] Safety outcomes were comparable between LAIV and IIV, irrespective of asthma severity.[86] The incidence of rhinitis was higher in those given LAIV but there was a lower incidence of hospital visits (inpatient or ED) compared with IIV.[86]

Data from the US also supported reviewing the precautions around the use of LAIV in children with asthma. No significant differences were shown between the frequency or severity of asthma symptoms for up to 42 days post vaccination when compared with QIV in 142 children aged 5 – 17 years. Sore throat and myalgia were more common in the LAIV group.[87]

LAIV was shown to be well tolerated in most children with asthma or recurrent wheeze, including those with severe or poorly controlled asthma in the UK.[88] A prospective phase 4 intervention study was conducted in 14 specialist asthma clinics. LAIV was administered under medical supervision to 478 children (median age 9.3 years, range 2 – 18 years). Of these children with asthma or recurrent wheeze, 44% received high-dose corticosteroids and 31% had severe asthma. No significant differences were shown in asthma symptoms for up to 4 weeks post vaccination (median change 0, $p = 0.026$). Severe asthma exacerbation requiring systemic corticosteroids was reported for 47 (15%) of the children and four cases occurred within 72 hours of vaccination. The rate of acute adverse events was in line with the reported rate in the normal population (0.6%).[88] The study found no evidence that LAIV administration resulted in an adverse event signal in young people with severe or 'difficult' asthma, including in preschool children with severe wheeze. The authors concluded that these findings support the UK guidance that 'children with asthma on inhaled corticosteroids (irrespective of dose) can be safely given LAIV', although it is not recommended in those with an acute exacerbation of asthma symptoms within the previous 72 hours.[88]

Children living with HIV infection

The National Advisory Committee on Immunization (NACI) in Canada conducted a systematic review of recommendations on the use of LAIV in children with HIV infection. Studies were limited, with only three studies reporting AEFI with LAIV in 191 children and young adults with HIV infection. These found the rates of AEFI were comparable between those with and without HIV infection. When compared with IIV, as previously reported, LAIV increased nasal congestion and rhinorrhoea. No serious AEFI were associated with LAIV in those with HIV and no AEFI were reported to Canadian AEFI surveillance system (CAEFISS) following LAIV in HIV-infected individuals. Vaccine virus shedding did not differ by HIV status.[89] NACI concluded that LAIV may be considered for certain children aged 2-17 years infected with HIV who are 1) receiving highly active antiretroviral therapy (HAART) for ≥4 months; 2) CD4 count ≥500/µl ages 2-5 years or ≥200/µl ages 6-17 years; 3) HIV plasma RNA <10,000 copies/mL. LAIV remains contraindicated for adults with HIV infection due to insufficient data.[89]

Summary

Potential responses to LAIV include nasal congestion, sore throat and rhinorrhoea, and in some cases headache and myalgia. Evidence suggests that it is not associated with exacerbation of underlying asthma or recurrent wheeze in children or adults aged from 2 to 49 years. No serious adverse events have been reported. LAIV may be considered for children with well-controlled HIV infection, but there is limited evidence to recommend its use in adults with HIV infection.

Immunogenicity

Recent evidence presenting immunogenicity data for LAIV is limited. Immunity induced by LAIV differs from that of IIV, which is unsurprising since LAIV induces a mucosal response using a whole influenza virus, as opposed to a more systemic response induced by intramuscular injection of subunit IIV. Reliance on peripheral blood antibody responses to measure immunogenicity may miss relevant mucosal antibody responses against respiratory viruses. Efficacy of LAIV is likely associated with IgA antibody responses within the nasal mucosa and $CD8^+$ T cell activation, which are not reflected in serum IgG antibody levels. In healthy adults (mean age 22 years), mucosal and blood antibody responses to LAIV were distinct and compartmentalised.[90]

Age and prior season vaccination play are role in the response to both QIVc and LAIV. Although HAI titres provide meaningful representation of vaccine response, they do not represent the full immune response. An RCT in the US used a multiplex influenza antibody detection assay (MIADA) with fluorescent bead technology to measure other immunoglobulins (IgG, IgA and IgM) against a range of different haemagglutinin epitopes and nucleoproteins in children and young adults (aged 4 – 21 years).[21] It found that QIVc induced higher HAI and IgG responses (but not IgM and IgA) than LAIV, but this varied by age and type of vaccine given previously. LAIV induced some level of serum HAI and IgG response, but the HAI response was minimal. Younger children had the highest HAI responses to LAIV (except for A/H3N2). Priming with LAIV induced a more robust response to QIVc in the following season.[21] The study did find that the MIADA immunoglobulin assay correlated strongly with HAI titres at day 28.

One study, which analysed data from a 2007/2008 FLUVACS RCT in adults aged 18 – 49 years, found that the efficacy of LAIV was not influenced by previous vaccination or baseline HAI or NAI titres. By contrast, previous vaccination and high baseline NAI titres significantly modified the efficacy of IIV.[91]

A Chinese study also found that HAI titres may not be as good a measure for LAIV immunogenicity in children as it is for IIV. Although LAIV is immunogenic in children aged 3 – 17 years, serum antibody responses tended to be lower than for IIV and data suggested that cellular and mucosal immune responses may play an important role in the immunity induced by LAIV.[92]

A UK phase 4 open-label study in 362 children aged 6 – 14 years examined whether pre-existing IgA or underlying viral upper respiratory tract infection had an impact on the immunogenicity of LAIV.[93] It observed no relationship between baseline nasal influenza-specific IgA and the fold-change in H1N1 or H3N2-specific IgG. The findings supported the annual use of LAIV, including in the presence of concurrent viral infections.[93]

Summary

Generally, the immunogenicity of influenza vaccines uses haemagglutinin inhibition assays to measure serum antibody levels, which are extrapolated to efficacy. For LAIV, this measure is less relevant and mucosal IgA and IgG responses are likely to influence immunogenicity and efficacy.

Efficacy and effectiveness

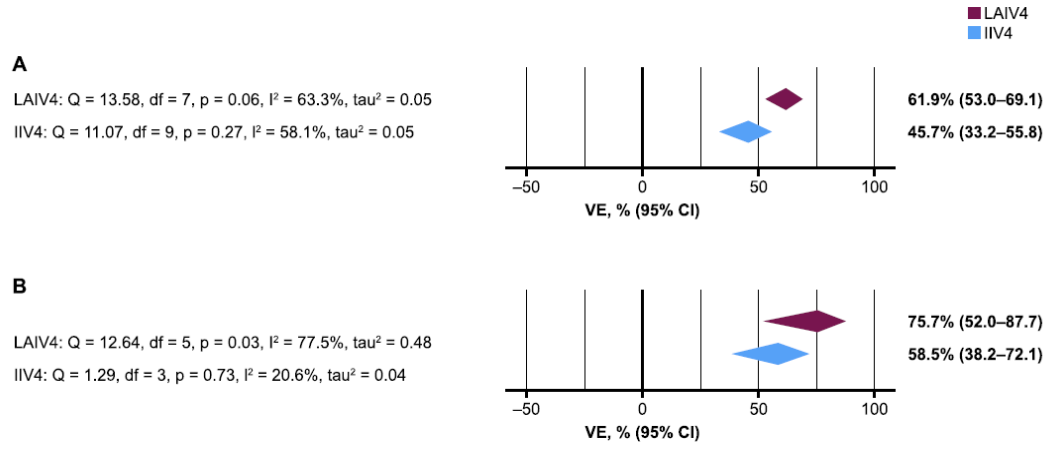
Currently, LAIV is only available in the Northern Hemisphere. Most studies have been conducted in the US, UK and Europe. Questions about the effectiveness were raised in the US during 2015/16 season with predominant A/H1N1pdm09.[6] LAIV was reported to be almost completely ineffective in preventing influenza in children aged 2-17 years in the US,[94] and the ACIP made an interim recommendation not to use LAIV for the 2016/17 influenza season.[95] Other countries, including the UK, Canada and Finland, did not record this loss of effectiveness and continued to recommend the use of the live vaccine with around 50% VE against A/H1N1 for 2016/17 season.[94] The US reinstated recommendations for LAIV in 2018/19 season.[96] Some countries continue to recommend LAIV preferentially in children over IIV (except for those contraindicated LAIV).

Presented here are some of the recent studies and systematic reviews on LAIV efficacy and effectiveness. See Table 12 for further details of the studies presented below.

Influenza infection

Bandell et al (2025, AstraZeneca) conducted a systematic review and meta-analysis of ten studies, across the 2019/2020 and 2022/23 influenza seasons in Europe and the US, to compare the effectiveness of LAIV4 with QIV in children aged 2 to 17 years.[97] The effectiveness of LAIV4 and QIV was moderate in children and generally comparable between vaccine formulations and seasons. Vaccine effectiveness against influenza infection for all strains was 62% (95% CI 52 – 69%) for LAIV and 46% (33 – 56%) for QIV (as shown in Figure 8). When compared by individual strains during the 2022/23 season, LAIV was 75% (53 – 88%) effective and IIV was 59% (38 – 72%).[97] It concluded that the results demonstrate influenza vaccination programmes are effective in children.

Figure 8: Meta-analysis of vaccine effectiveness of LAIV4 and QIV against a) all influenza infection in children during 2019/202 to 2022/23 seasons, and b) by strain (all strains) in the 2022/23 season (Bandell, 2025, open access)



Another AstraZeneca systematic review presented real-world effectiveness of LAIV in children aged ≤18 years in comparison to IIV against any seasonal influenza over three time periods:[87, 88]

- 2003/4 to 2008/9 prior to the A/H1N1pdm09 influenza pandemic (8 studies, IIV only)
- 2010/11 to 2016/17 following A/H1N1 pandemic (76 studies)
- 2017/18 to 2022/23 following an update to the LAIV strain production process (34 studies).[98, 99]

For both vaccines, effectiveness varied across season with adjusted vaccine (aVE) effectiveness point estimates that varied from 30% – 66% for LAIV and 28% – 72% for IIV with wide, overlapping confidence intervals. Effectiveness was generally comparable between vaccines, with some years one outperforming the other. During 2017/18 and 2019/20, LAIV was more effective against influenza B in children than IIV (81% vs 49%) but equivalent in 2022/23. While fluctuations occurred, effectiveness of around 50% was seen for both vaccine in children against all influenza.[98]

Influenza-associated hospitalisation

Using a screening method of vaccine coverage, the overall effectiveness of LAIV against influenza-hospitalisation was shown to be around 50% (95% CI 31 – 64%) in children aged 2 – 6 years in the UK over three influenza seasons.[100] Hospitalised children were compared with children in the general population. A total of 277 cases were hospitalised with laboratory-confirmed influenza during the first three seasons of the UK LAIV programme in preschool children. Of the cases, 55 (24%) were vaccinated including 53 given LAIV. Early in the programme, only preschool children were vaccinated, in the 2015/16 season, both preschool and school children in year 1 and 2 (ages 5 – 6 years) were routinely vaccinated. For 2015/16, the adjusted vaccine effectiveness was 49% (23 – 67%) in preschool children and 63% (3 – 86%) in 5 – 6-year-olds.[100]

A sensitivity analysis of children aged 2 – 4 years with influenza risk-group status found that almost 70% were unvaccinated and of those vaccinated 57% had missing information on risk-group status. Adjusted vaccine effectiveness against hospitalisation in those with known risk factors was 44% (3.3 – 68%) and increased to 70% (58 – 79%) in those with unknown risk but assumed to have a risk factor compared with 58% (34 – 73%) for those with unknown risk but assumed no risk factor.[100]

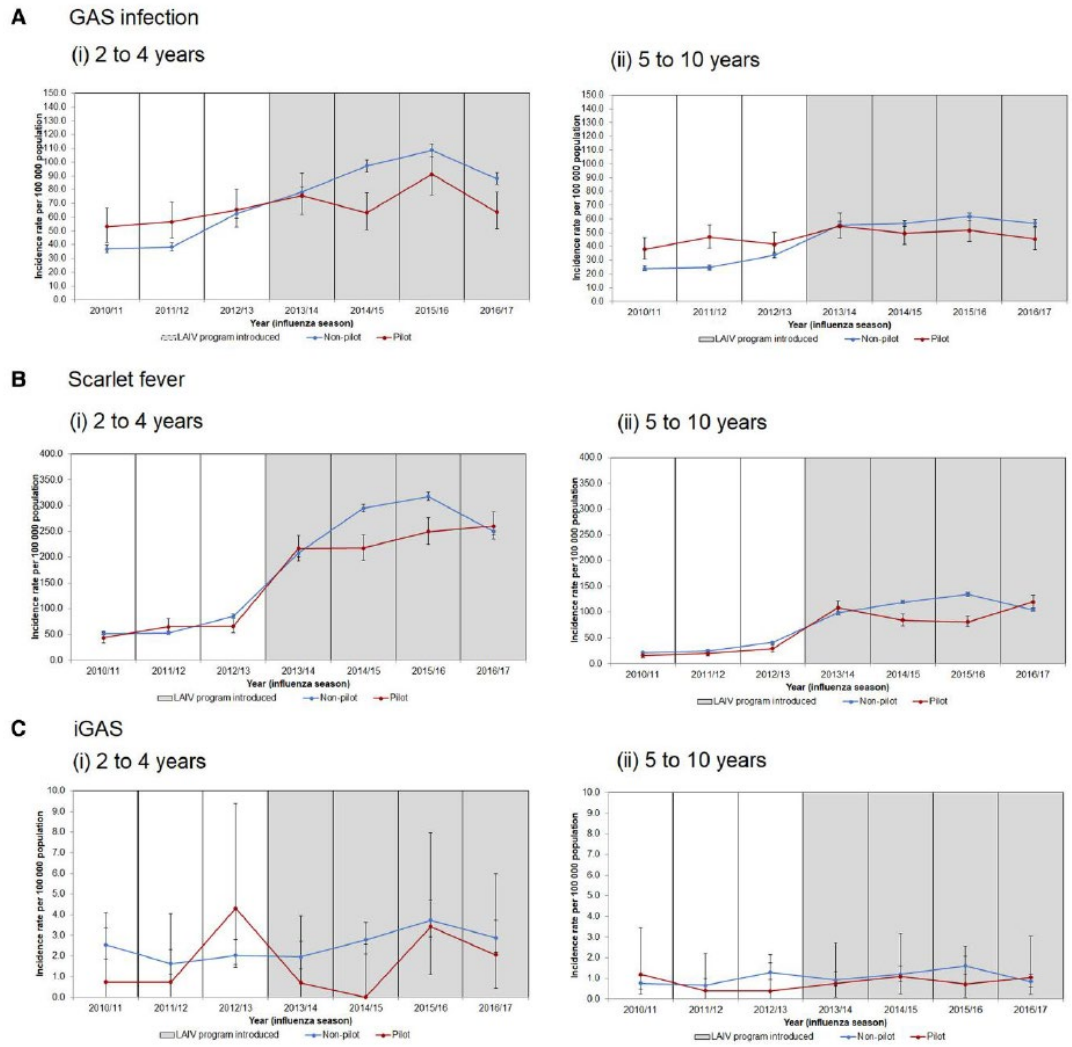
LAIV was moderately effective (64%) in preventing influenza-related hospital contact and hospital admission (37%) of young children but appeared to be less able to prevent secondary outcomes of influenza infection.[101] A cohort study in Denmark used nationwide health-care registries of 95,434 children aged 2 – 6 years vaccinated with two doses of LAIV during 2021/22 season (an H3N2 predominant season) and compared with 95,434 unvaccinated controls. The incidence rate ratio (IRR) was 0.36 (76 vs 210 events) for influenza-related hospital contacts vaccinated with LAIV4 compared with no vaccine, with an estimated vaccine effectiveness of 64% (95% CI 54% – 73%). Vaccine effectiveness for influenza-related hospital admission (for >12 hours, based on 24 vaccinated and 38 unvaccinated cases) was 37% (-5.2 to 62%). Effectiveness was similar for children with or without coexisting influenza risk factors.[101]

However, LAIV was not associated with a reduction in respiratory tract infections (IRR 1.14, 0.94 – 1.38), wheeze or asthma (1.04, 0.83 – 1.31), or antibiotic prescriptions for any respiratory infection (IRR 0.97, 0.93 – 1.0). It was noted that the study was not designed to determine differences in severity for these outcomes, beyond the need for hospitalisation, and did not differentiate influenza from other respiratory pathogens for these outcomes.[101] Furthermore, false positives for influenza virus testing in the first few weeks after vaccination resulted in an underestimation of effectiveness. When a sensitivity analysis disregarded influenza-related outcomes for the first 30 days after vaccination, VE increased to almost 70% (60 – 77 %) for hospital contacts and 53% (17 – 73%) for hospital admissions.[101]

Unlike the study above, a secondary impact of LAIV has been seen in Group A streptococcus (GAS) infections in the UK.[102] Cumulative incidence of GAS infections, scarlet fever and invasive GAS infections in children aged 2 – 4 and 5 – 10 years in England were compared during influenza seasons, pre and post the LAIV pilot programmes, and between pilot areas and non-pilot areas. As

shown in Figure 9, a reduction in influenza in children through LAIV vaccination likely contributed to reductions in secondary bacterial infections. The most significant impact was seen in 5 – 10-year-olds, which have the highest burden of GAS infections, with a cumulative decrease in GAS infections from pre to post LAIV programmes for pilot vs non-pilot areas (IRR: 0.57, 0.45 – 0.71, p<0.001).[102] The study did not identify significant differences in non-target age groups, in whom, the differences varied and were minimal.

Figure 9: Incidence rate ratios of GAS infections (invasive and non-invasive) per 100,000 population of (95% CI) by LAIV pilot and non-pilot areas and influenza season for targeted age groups (Sinnathamby, 2023, open access)



Adults

Limited studies have evaluated the efficacy of LAIV in adults. Results of a systematic review of 22 studies (Perego et al 2021) supported LAIV over placebo, but a meta-analysis showed lower efficacy than IIV. No RCTs were found evaluating LAIV in high-risk participants, such as breastfeeding, immunocompromised, aged over 65 years or frail elderly, and healthcare workers.[103] The authors recommended that further reviews of efficacy and vaccine acceptance were necessary.

Summary

Real-world effectiveness of LAIV of around 50% is at least equivalent to that of IIV, particularly against infection in children aged 2 – 17 years and hospitalisation in children aged 2 – 6 years. Slightly higher effectiveness was seen against influenza B. One systematic review found effectiveness against infection of around 62% with higher effectiveness of 75% when effectiveness against individual influenza strains is evaluated. However, effectiveness against hospitalisation was suggested to be higher (at 70%) due to false-positive detection of shed vaccine virus in the first month after vaccination. Further studies are required to determine whether LAIV has an impact on influenza-related outcomes or severity. Data is limited on the use of LAIV in adults.

Broad coverage influenza vaccination, such as provided by LAIV in UK school children, may also reduce the risk of secondary bacterial infections. If high coverage could be achieved in New Zealand, it could also help to reduce the high incidence of invasive group A streptococcal infections and associated rheumatic heart disease in children. With similar effectiveness to IIV, intranasal LAIV may be more acceptable and encourage a greater vaccine uptake in children, which in turn may improve influenza control and the overall effectiveness of the influenza immunisation programme.

Summary of evidence

Table 8: Cell-based influenza vaccine

Outcomes	Ref	Study type / Participants	Results	Findings
Safety				

Systematic review	13	SR, literature to Feb 2020 use in adults aged ≥18 years	• Local reactions
			  ○ No significant differences for pain, redness, swelling, induration between cell and egg-based TIV.
			  ○ Ecchymosis (bruising) significantly higher rates for cell-based (RR 1.27; 95% CI 1.03-1.56, 3 RCT, low certainty.
			  ○ Similar results in older adults
			• QIVc vs TIVc and TIVc vs placebo – increase rate of injection site pain
			  ○ systemic reactions
			  ○ No significant difference between TIVc and TIVe
			• Uncontrolled study noted increased reactions in younger adults (18-61y vs >61y)
				Cell-based vaccines are well tolerated in adults and have a similar safety profile to egg-based influenza vaccines.

Enhanced passive safety surveillance	14	Summary safety surveillance over 3 seasons (2019/2020 to 2021/2022), in Genoa, Italy. (conducted in collaboration with Seqirus) Age range: 2019/20 and 2020/21 from age 9 - ≥65 y, 2021/22 from aged 2 - ≥65y.	• Based on 3,603 QIVc exposures recorded in passive surveillance. • Rate of individual case safety reports reduced with time (p = 0.002: 1.75%, 0.48%, 0.40% in each year) • On average around 3.5 AE per report, (35/10, 19/5 and 13/4, per year) • Similar AE across all age groups. Only 1 report in paediatric group (local reaction), alongside low coverage. One case of anaphylaxis considered vaccine related. • No safety signals identified. Most adverse events were reactogenic – include fever, malaise, injection site pruritus. All AE were below expected rates (<0.5% for all).	No safety signal was identified by enhanced passive safety surveillance of QIVc vaccination over three influenza seasons. These findings confirmed the safety profile presented in the product safety information.

Clinical trial in children aged 6 to 47 months	15	Phase 3 RCT, observe blind QIVc vs QIVe in US, 2019-2020 influenza season.
		2402 children aged 6-47m: 894 (37.2%) aged 6-23m and 1,508 (63%) aged 24-47m
			• Solicited AE
			  ○ Any: 65.9% QIVe and 63.7% QIVc
			  ○ Local: 44.6% vs 41.9%
			  ○ Systemic: 45.7% vs 43.5%
			  ○ Analgesia or antipyretic use: 17.3% vs 15.3%
			• Medically attended AE – 12% vs 13.9%
			• 0 related serious AE; 2 deaths in QIVc group (neither vaccine related)
				No clinically meaningful differences between cell-based or egg-based QIV, as seen with older children and consistent with other QIVs in this age group.

Outcomes	Ref	Study type / Participants	Results	Findings
Safety in children aged 2 to <18 years	16	RCT over 3 flu seasons in 8 countries. QIVc compared with MenACWY 4514 participants enrolled (mean age 8.8 ± 4.1 years). 65.9% had received a flu vaccine previously.	Incidence of AE similar between groups: • Between 6 h and 7d after vaccination – 51.4% QIVc and 48.6% comparator group reported solicited AE. • Patterns of local and systemic AE were similar between groups • Fever – ≥38°C 5.3% vs 4.5%; ≥40°C 0.3% vs 0.2% • No SAE were considered vaccine related.	Safety profile of QIVc was similar to that of MenACWY vaccine in children from age 2 years. Around half of the children experienced at least one solicited local or systemic adverse reaction within 7 days of vaccination. None were considered serious.
Post market surveillance, health care workers	18	AEFI within 7 days post QIVc, Italy. 1481 HCW given QIVc during 2019/20 influenza season. 775 volunteers in surveillance programme, 55.6% female. Average age 41.3 ± 14.1 years (51.3% <40y)	741 out of 775 reported ≥1 AE (95.6% response rate). Most resolved within 2 days. • Local AEFI – 87.% (of which pain at injection site made up 94.4%, within 2 days) • General malaise – 26.5% (at 1 day) • Neurological symptoms – 8.4% • Fever – 4.8% • GI disorder – 2.1% • Allergic reaction – 0.4% • 1 SAE – considered viral infection not vaccine related. Females reported more AEFI than males (local, malaise and fever) and younger people had more local and GI disorders.	Good safety profile of QIVc in health care workers.
Immunogenicity				
Comparison cell and egg-based QIV in children	15	Phase 3 RCT, observe blind QIVc vs QIVe in US, 2019-2020 influenza season. 2402 children aged 6-47m: immunogenicity in 1092 QIVc and 575 QIVe	GMTR QIV:QIVc (upper bound 95% CI) – did not exceed 1.5 • A/H1N1 – 0.73 (0.84) • A/H3N2 – 1.04 (1.16) • B/Yamagata – 0.73 (0.81) • B/Victoria – 0.88 (0.97) Seroconversion differences (QIV-QIVc) did not exceed 10% for 4 virus strains • A/H1N1 = -11.46% (-6.42) • A/H3N2 = 3.13% (7.81) • B/Yamagata =-14.87% (-9.98) • B/Victoria = -5.96% (-1.44)	Immune responses to cell-based QIV were similar to the licensed egg-based QIV in children aged 6 to 47 months.

Outcomes	Ref	Study type / Participants	Results	Findings
	19	RCT comparing QIVc with QIVe in 144 healthy children aged 4-20 (median 14) years during 2018/19 season in US. Blood samples taken day 0 and 28 (19-35) days post vaccination. 2018/19 QIVc contained cell-based strains for A/H3N2 and B/Victoria, B/Yamagata. A/H1N1 was egg-based. 2017/18 – only A/H3N2 was cell-based.	• No significant differences between groups for seroconversion rates or elevated titres. • Except HI mean fold rise (MFR) for A/H3N2 was significantly higher in QIVe recipients (2.3; 1.8-2.9) vs QIVc (1.6; 1.3-2.0; p=0.05) Day 0 – more than half of children had elevated HAI (A/H3N2, A/H1N1 and B influenza viruses) or microneutralisation (A/H3N2 only egg and cell grown strains) titres. Post-hoc analyses - majority (62%) had received QIVe in previous season, remainder were unvaccinated. • generally, MFR was greater for those unvaccinated in 2017/18 season than those vaccinated in that season. • A reduced response to QIVc against H1N1 and H3N2 cell-grown virus and QIVe for B/Vic after controlling for baseline.	Seroconversion, seropositivity and fold-rise did not differ significantly at day 28 post vaccination with QIVc or QIVe.
Peripheral immune activation in children	20	Samples taken from study above. RNA sequence on day 0 and day7 was paired with antibody for 81 participants (40 QIVc and 41 QIVe).	No significant difference in seroconversion for H1N1, H3N2 or B/Vic. Greater seroconversion against B/Yama for QIVe vs QIVc IFN type 1 response, IFN-γ-mediated signalling, cytokine activity, and regulation of T-cell activation, all suppressed in recipients of QIVe versus QIVc.	These data suggest cell-based influenza vaccines differ in how they stimulate immunity from egg-based vaccine, despite similar HAI antibody induction. Analysis showed QIVc induced greater IFN signalling and innate immune activation than QIVe. Those who seroconverted to ≥1 influenza vaccine strain had higher IFN signalling than those who didn't, regardless of vaccine type. Activating different arms of the immune system, beyond antibody production may improve vaccine effectiveness.
Cell-based vs LAIV in children	21	RCT, participants aged 4-21 years in US; 112 received QIVc and 118 LAIV. Multiplex influenza antibody detection assay (MIADA) and HAI pre and 28 days post vaccination.	• HAI and immunoglobulin isotype response to QIVc > LAIV, significant increases in IgG but not IgM or IgA. • Youngest had highest LAIV response. • Prior LAIV associated with higher current season QIVc response. • Immunoglobulin assays correlated strongly with and confirmed HAI titres and MFI values for both vaccines. • Immunoglobulin assays can detail a range of responses to different regions of HA epitopes (head, stalk, and cross-reactivity) and nucleoprotein antigens.	Age and prior season vaccination play a role in the immune response in children and young adults to both QIVc and LAIV. HAI titres can provide meaningful representation of day 28 response to vaccination but does not represent the full immune response. QIVc induced higher HAI and MFI than LAIV, but varied by age and type of vaccine given previously
Effectiveness				

Outcomes	Ref	Study type / Participants	Results	Findings
Systematic review comparing cell- and egg-based IIV	22	Seqirus SR, effectiveness 18 publications over 3 seasons (2017-2020). QIVc compared with no vaccination or standard dose TIVe or QIVe In 2018/19 season, A/H1N1 vaccine virus in the QIVc was not cell-based. In 2019/2020 all vaccine strains were produced in cells.	pooled relative effectiveness (rVE) against any medical encounter related to influenza and/or laboratory-confirmed influenza • Overall: 8.4% (95% CI 6.5-10.2) for QIVc vs TIVe/QIV. • Ages 4-64 years: o 2017/2018 = 16.2% (7.6-24.8%) o 2018/19 = 6.1% (4.9-7.3%) o 2019/20 = 10.1% (6.3-14.0%) • Ages ≥65 years o 2017/18 = 9.9% (6.9-12.9%) o 2018/19 = 0 difference	For younger people, ages 4 – 64 years, cell-based QIV was consistently more effective relative to egg-based vaccines over three seasons. In those aged over 65 years, seasonal variation meant some difference some years but not others. Seasonal variation in predominant influenza types and egg-adaptation of vaccine virus likely affected the results.
Effectiveness in high-risk groups	23	*Included in systematic review above* 471,301 received QIVc compared with 1.64 million QIVe Seqirus funded study	Relative effectiveness of QIVc vs QIVe against influenza-associated medical encounters • ≥1 health condition: 13.4% (11.4-15.4%) • Chronic pulmonary disease: 18.7% (16.0-21.3%) • Rheumatic disease: 11.8% (3.6-19.3%)	Data support the use of cell-based QIV in individuals aged 4 years and over with at least one underlying health condition, with evidence of improved effectiveness over egg-based QIV.
Relative effectiveness cell-based vs egg-based in children and adolescents	24	*Included in systematic review above* Retrospective database link EMR, medical and pharmacy claims US children aged 4 - 17 years 2019/2020 season. 60,480 received QIVc and 1.24 million QIVe. Seqirus funded.	Relative VE against IRMEs QIVc vs QIVe Any encounter – 12.2% (7.5-16.6) Outpatients – 14.3% (9.3-19.0) Inpatients– infrequent (≤1%), Null rVE	Cell-based QIV was associated with a greater reduction (of around 12%) in influenza related medical encounters of children than egg-based QIV.
Effectiveness against H3N2	25	*Included in systematic review above* Test-negative HAIVEN study. 6129 adults from 10 hospitals 2016/17 and 2017/18 – high A/H3N2 hospitalisations despite match with vaccine strain.	Adjusted VE against PCR confirmed influenza hospitalisation: • All influenza over both years – 33.5% (23.6-42.0) • A/H3N2 – 22.8% (8.3-35.0%) – pooled both years o Point estimate QIVc = 43.0% (-36.3 to 76.1, n=56) o Vs QIVe = 24.0% (3.9 – 39.99%) (similar findings if exclude high dose) • B/Yamagata – 49.4% (34.3-61.1%) • In both seasons, increasing HAI antibody against egg-adapted A/H3N2 [Hong Kong/4801/2014) vaccine strain was associated with protection, which was inconsistent with low vaccine effectiveness.	Low vaccine effectiveness (<25%) against hospitalisation when the same vaccine virus was used in both A/H3N2 seasons, even in years with a good antigenic match, emphasised continual changes in the H3N2 antigenic epitopes. (due to glycosylation of antigenic sites from egg-adaptation to allow propagation in eggs, not required for generation of cell-grown seed virus).

Outcomes	Ref	Study type / Participants	Results	Findings
Comparative effectiveness in ≥65-year-olds	26	*Included in systematic review above*; retrospective cohort study comparing egg-based hd-TIV, aTIV and QIV, cell-based QIVc and RIV4. 12.7 million Medicare beneficiaries aged ≥65 years A/H1N1 and B-Vic dominated season 2019/2020 Seqirus funded study	Adjusted IPTW analysis, rVE against influenza hospital encounters vs standard QIVe: • RIV4: 13.3% (95% CI, 7.4–18.9%) • aTIV: 8.2% (95% CI 4.2–12.0%) • hd-TIV: 6.8% (95% CI, 3.3–10.1%) • QIVc: 2.8% (95% CI −2.8%, 8.2%) – not significantly different	In this study, with an A/H1N1 predominant season, there was no significant difference between cell-based and egg-based inactivated influenza vaccines in adults aged 65 years and older.
Efficacy in children aged 2-<18 years	16	RCT over 3 flu seasons in 8 countries. QIVc compared with MenACWY 4514 participants enrolled (mean age 8.8 ± 4.1 years). 65.9% had received a flu vaccine previously. Two doses given 28 days apart to those who hadn't received influenza vaccine previously or comparators given placebo as dose 2. (Seqirus funded study)	• Laboratory confirmed (PCR or culture) influenza occurred in 175/2257 (7.8%) QIVc group and 364/2252 (16.2%) comparators. • Influenza, any strain VE 54.6.7% (95% CI 45.7 – 62.1) • Culture confirmed influenza, antigenically matched strains 63.6% (53.6-71.5) • A/H1N1 – VE 80.7% (69.2-87.9) • A/H3N2 – VE 42.1% (20.3-57.9) • Influenza B – 47.6% (31.4-60.0)	Cell-based influenza vaccine provided protection to healthy children and adolescents against influenza.

Cell vs egg 3 seasons in ages 4-64 years	27	Retrospective test-negative design study. Ages 4-64 years over 3 influenza seasons (2017-2020) in US.
		31,824, 33,388 and 34,398 patients over 3 years. Approx 10% received QIVc and 90% received QIVe.
		(Seqirus funded study)
			• Test-confirmed influenza (tested as part of routine care for febrile ARI) relative effectiveness (rVE)
			  ○ 2017/19 = 14.8% (7.0-22.0%) [vaccine A/H3N2 cell-derived]
			  ○ 2018/19 = 12.5% (4.7-19.6%) [vaccine A/H1N1 and B cell-derived]
			  ○ 2019/20 = 10% (2.7-16.7%) [all 4 strains cell-derived]
			2019/20 season truncated Sept-Mar, instead of May due to COVID-19.
				Study reported superior effectiveness of cell-based vs egg-based influenza vaccine over 3 seasons.

Systematic review in adults ≥18 years.	13	SR, literature to Feb 2020 use in adults aged ≥18 years. Two efficacy and 4 effectiveness studies included.	Pooled estimate for efficacy for QIVc – 2 RCT • for any influenza - 70% (95% CI 61–77%), I^2 = 0%, moderate-certainty • A/H1N1= 82% (71–89%) I^2 = 62%, moderate-certainty • A/H3N2 = 72% (39–87%) I^2 = 0%, moderate-certainty • Influenza B= 53%, (30%–68%) I^2 = 0%, moderate-certainty Pooled estimated for effectiveness (3 test-negative studies, one cohort study) • Inconsistent findings by season, outcomes and comparator (IIVe or no vaccination).	High-quality evidence for efficacy and effectiveness were lacking. The limited evidence from a single influenza season suggested that effectiveness might be slightly better for cell-based vaccines. In some cases, where described, , an egg-based seed virus was used to produce cell grown virus. Therefore, further studies are required using purely cell-grown virus to confirm whether avoidance of egg-adaptation can improve effectiveness of cell-based influenza vaccines.

Outcomes	Ref	Study type / Participants	Results	Findings
VE in 2022/23	29	Test-negative design study in primary care in GB, 2022/23 season predominantly A/H3N2 and A/H1N1 cocirculation. Influenza B late in season. Total 2,445 cases, 10,635 controls. OR odds of being vaccinated between cases and controls VE = (1 – OR) x 100 Vaccination may not have been recorded if given in the workplace which might have affected data for 18-64 years as not universally funded vaccine (just high-risk adults)	• VE against all lab-confirmed influenza • Age ≥65 years mostly aQIV o All influenza 30% (-6 to 54%); no data for QIVc o A/H1N1 = 5% (-87 to 52%) o A/H3N2 = 35% (-11% to 62%) o B – too few detections • Ages 18-64 years (mostly QIVc) o All influenza VE QIVc = 48% (37-57%) (of vaccinated n= 1724 flu- and 242 flu+) QIVe= 26% (-32-58%) (n=83 flu- and 19 flu+) o A/H1N1 = 42% (23%–56%) o A/H3N2 = 37% (21%–50%) o B = 71% (49%–84%) • Ages 2-17 years, mostly LAIV (n= 455 flu- and 52 flu+) o All flu= 68% (55-78%); overall 66% (53-76) o H1N1 = 73% (43-87%) o H3N2 = 59% (40%–72%) o B = 95% (62%–99%) (<3 cases vaccinated vs 44 unvaccinated)	VE estimates in adults age ≥65 years were positive but non-significant for influenza A. Moderate effectiveness against H3N2 overall, in children and adults aged 18-64 years. Low to moderate effectiveness against A/H1N1pdm09 (same vaccine strain as used in 2021/22 season). Noted late delivery of LAIV in England, may have impacted protection against A/H3N2 which circulated early.
Cell vs egg QIV in ages 18-64 years against influenza hospitalisation	30	Retrospective KPSC cohort study. Received ≥1 dose influenza vaccine aged 18-64 years (n=848,334). (Moderna funded study)	• Incident rates of influenza hospitalisation / 1000 person years: o Age 18-49 years: QIVc = 0.2 (0.1-0.4) and QIVe = 0.2 (0.2-0.3) o Ages 50-64 years: QIVc = 0.2 (0.1-0.4) and QIVe = 0.3 (0.2-0.4) • Adjusted cVE against hospitalisation : o Ages 18-49 y = -10.1% (-49.8 to 37.8%) o Ages 50-64 years = 14.9% (-33.8% to 52.1%).	Cell based and egg-based influenza vaccines provided comparable protection against influenza-associated hospitalisation in adults aged 18-64 years during 2022/23 season in California.
Relative effectiveness cell-based vs egg-based in adults	28	*Included in systematic review above* Retrospective cohort - ≥18 years during 2019/2020, 1.5 million received QIVc vs 4.1 million QIVe Seqirus funded study	Relative VE of QIVc vs QIVe • against influenza-related medical encounters (not lab-confirmed, but peak of season) o any – 9.5% (95% CI 7.9-11.1%) o inpatient – 5.7% (2.1-9.2%) o outpatient – 11.4% (9.5-13.3%) • Inpatients by age group o All ages ≥18y= 5.7% (2.1 – 9.2%) o 18-64y = 5.8% (1.9 – 9.5%) o 18-49 = 6.6% (1.6 –11.3%) o 50-64y = 5.2% (–0.9 to 11.1%) o ≥65 y = 5.3% (–4.9 to 14.5%) • Outpatients by age group o All ages ≥18y= 11.4% (9.5-13.3%) o 18-64y = 14.7% (12.7-16.7) o 18-49 = 16.2% (13.5-18.7%) o 50-64y = 13.0% (9.8-16.1%) o ≥65 y = -14.6% (-20.5 to -8.9%)	Cell-based QIV was associated with relatively fewer influenza-related medical encounters than egg-based QIV in adults aged 18 – 64 years during the 2019/2020 influenza season in the US. There was no difference in vaccine effectiveness for older adults aged 65 or over.

Outcomes	Ref	Study type / Participants	Results	Findings

Relative effectiveness cardiorespiratory hospitalisation	31	Retrospective cohort study with linked electronic medical records during 2019/2020 season in US Aged 18-64 years (80.4% of total cohort)
		1.49 million (25%) received QIVc and 4.41 million received QIVe (75%).
		Inverse probability of treatment weighting (IPTW) odds ratios to calculated relative VE 100(1-adjOR)
		(Seqirus funded study)
			Aged 18-64 years
			QIVc rVE against hospitalisation for any diagnosis of :
			• Cardiorespiratory overall rVE = 2.5% (0.9-4.1%)
			• Respiratory = 3.7% (1.5-5.8%)
			  ○ Influenza (not laboratory confirmed) = 9.3% (0.4-17.3%).
			• No difference for other outcomes (pneumonia, myocardial infarction, ischaemic stroke)
			When look at age groups:
			• 18-49 years, any hospitalisation diagnosis of respiratory rVE = 6.7% (3.8-9.5)
			  ○ Influenza – 11.9 (-4.9 to 26.0)
			  ○ No difference for cardiac outcomes or pneumonia
			• 50-64 years – rVE cardiorespiratory = 0.1 (-1.8 to 2.0)
			  ○ Influenza = 8.1 (-2.6 to 17.7)
			  ○ Myocardial infarction = 9.4 (2.5 to 15.8)
				The greatest difference between cell-based and egg-based QIV was seen against influenza hospitalisation in ages 18-64 years. In the overall population, no differences were seen between the vaccines for myocardial infarction or stroke, but in the 50–64-year-old group cell-based vaccine was favoured against myocardial infarction.

Outcomes	Ref	Study type / Participants	Results		Findings
Effectiveness and impact in children and adults	[32]	Seqirus retrospective analysis, test-negative design study, comparing QIVc and QIVe in the US 2023-2024 season. Using linked dataset provide by HealthVerity, almost 17 million received QIVc or QIV3, a total of 106,779 met eligibility criteria. • 57% paediatrics (6m-17y). • 54% had ≥1 high risk condition (37% paediatric, 75% adult) • Median age: QIVc 29.6 (SD 22.3), QIVe 22.3 (SD 21.2) years. Cases younger than controls, on average. confirmed influenza with a valid influenza test within 7 days of acute respiratory or febrile illness. a/H1N1pdm09 most prevalent, A/H3N2 and B/Vic later in season.	QIVc group: 2,119 (13%) cases and 14,750 (87%) negative controls QIVe group: 14,559 cases (16%) and 75,351 (84%) controls Adjusted relative effectiveness: • overall rVE 19.8% (15.7 – 23.8%) • age 6m – 17y rVE 19.6% (13.6-25.3%) ○ 6m – 8y rVE 17.6% (9.3-25.1%) (67% of children) ○ 9y – 17 rVE 23.3% (15.1-32.5%) (33% of children) • age 18-64 y rVE 18.5% (12.1-24.5%) • high risk ≥1 condition: ○ any age 14.7% (8.7-20.3%) ○ age 5-64 years 17.1% (10.9-22.9%) ○ adults 17.1% (9.3-24.1%) • Influenza A rVE 19.3% (14.0-24.2%) • Influenza B rVE 36.8% (30.0 – 42.9%)(tended to be younger, highest prop age 5-17y and less likely to have ≥1 underlying condition)	Applying rVE to previously published base case aVE for QIVe gives aVE for QIVc (aVE difference QIVc vs QIVe) • age 6m-4y 61% (9%) • 5-17y 67% (8%) • 18-49y 49% (11%) • 50-64y 32% (16%) Burden-averted model estimated over 2.3 million fewer symptomatic illness, >14,000 hospitalisations and > 500 deaths would have been prevented if all aged 6m – 64 years received QIVc. Compared with QIVe, QIVc controls older, more high risk and insured – weighting balanced covariates overall. QIVe – estimated averted cases 7.2 million symptomatic cases and 34,382 hospitalisation, 880 deaths. QIVc – estimated averted cases 9.5 million symptomatic cases, 49,312 hospitalisations and 1455 deaths.	Relative effectiveness of QIVc was almost 20% higher than QIVe during the 2023/2024 influenza season in the US against symptomatic, confirmed influenza in individuals aged 6 months to 64 years. Provided evidence of improved effectiveness in paediatric population from age 6 months. Influenza vaccine averted millions of cases. Incremental benefit of QIVc vs QIVe estimated a further 2.3 million symptomatic cases, over 14,000 hospitalisation and over 500 deaths.

Abbreviations: AE – adverse events; AEFI – adverse events following immunisation; 95% CI – 95% confidence interval; EMR – electronic medical records; GB – Great Britain; GI – gastrointestinal; HA – haemagglutinin; HAI – haemagglutinin inhibition assay; hd-TIV – high-dose trivalent influenza vaccine; IFN – interferon; IPTW - inverse probability of treatment weighting; IRME – influenza-related medical encounter; KPSC – Kaise Permanente Southern California; LAIV – live attenuated influenza vaccine; m – months; MenACWY - meningococcal groups A, C, W, Y vaccine; MFI – median fluorescent intensity; MFR – mean fold rise; MIADA – multiplex influenza antibody detection assay; QIV – quadrivalent influenza vaccine; QIVc – cell-based quadrivalent influenza vaccine; QIVe – egg-based quadrivalent influenza vaccine; RCT – randomised controlled trial; rVE – relative vaccine efficacy/effectiveness; SAE – serious adverse events; SR – systematic review; TIV – trivalent influenza vaccine; TIVc – cell-based trivalent influenza vaccine; TIVe – egg-based trivalent influenza vaccine; US – United States [of America]; VE – vaccine efficacy/effectiveness; vs – versus; y - years

Table 9: Adjuvanted influenza vaccine

Outcomes	Ref	Study type / Participants	Results	Findings
Safety				
Enhanced passive surveillance	[35]	As above, Italian EPPS in 2015, 2016 and 2017 given Fluad (aTIV). 1060, 1046 and 1045 participants.	• Spontaneous AE – 0.5%, 0.7% and 0.5% in 2015, 2016 and 2017 respectively. • Most AE were mild-to-moderate in severity • No differences between seasons. • Two serious AE: backpain in 85 yo woman was deemed temporally but not causally related to vaccine and cerebral haemorrhage	Most adverse events following vaccination with adjuvanted influenza vaccine were mild to moderate in severity and were consistent with the safety profile of the vaccine observed over 20 years of use.
Enhanced passive safety surveillance	[36]	2021/22 season in Italy. Participants reported AE via vaccination cards 7 days post vaccination with aQIV. 1059 participants aged ≥65 years.	• On non-serious AE reported (0.9 / 1000 doses) – pyrexia, associated with other AE feeling hot, pain at extremities, generalised pain and insomnia (in patient with lymphoma) • Consistent with previous aTIV and with RCT data.	No safety issues regarding aQIV were identified and were consistent with data for any influenza vaccine in the same year in Italy (0.5 AEFI /1000).

Coadministration with recombinant zoster vaccine (rZV)	[39]	RCT (NCT05007041) blinded conducted during 2021/22 and 2022/23 influenza seasons in US among 271 community-dwelling adults aged ≥65 years (median age 71 years, range 65-92), comparison of aQIV or hd-QIV with rZV given IM in opposite arms. >90% white participants.	• 130 participants received aQIV and rZV
			• 15/115 (11.5%) patients reported ≥1 severe solicited reactogenicity AE
			  ○ 8/122 (6.2%) reported ≥1 severe solicited local reactogenicity AE
			  ○ 7/123 (5.4%) reported ≥1 severe solicited systemic AE
			• Also non-inferior difference between groups after 2nd dose RZV alone.
			• Clinically similar patterns of SAE among ages 65-70 y and >70 years
			• During 43-day follow-up period, there were not cases of GBS or deaths.
			• 1 SAE – left partial cranial nerve III palsy was possibly related to RZV and hd-QIV
				No significant difference between groups. Study supports safety for coadministration of aQIV and rZV among older adults. Findings were consistent with previous studies using standard QIV and rZV concomitantly.

Coadministration with RSV vaccine	[40]	Phase 3 RCT, open label, in EU and UK. Adjuvanted RSVpreF (Arexvy) and aQIV coadministered or sequential admin (aQIV then RSV, 1 month apart) 1045 participants aged ≥65 years (mean age 72 years)	• Most frequent solicited AE, median duration ≤2 days:
			  ○ local Pain on aQIV side = Coad 51.7%, control 44.8%
			  ○ Pain on RSVpreF side = Coad 66.1%, control 58.8%.
			  ○ Fatigue = 45.7% coad vs 28% aQIV and 30.4% RSVpreF
			  ○ Myalgia = 39% coad vs 23% aQIV and 31.9% RSVpreF
			Most common unsolicited AE considered vaccine related was myalgia CoAd groups and fatigue, headache, influenza-like illness in control group (0.4% each)
			1 case of Giant cell arteritis considered as potentially vaccine related.
			No reports of GBS or other neurologically related AESI.
			No deaths associated with vaccination.
				The safety profile following coadministration of RSV and adjuvanted influenza vaccines was deemed clinically acceptable and well tolerated. Systemic solicited AE were more frequently reported after coadministration than sequential administration, but there was no increase in severity or duration of these events, and rates of all AE were balanced between the groups.

Coadministration with mRNA COVID-19 vaccine	[41]	SR conducted April 2022, 5 studies. 3 clinical trials compared safety and immunogenicity of coadministration with separate admin.	Four flu vaccines (aTIV, QIVc, hd-QIV, RIV4) and 4 COVID-19 vaccines included (adenovirus-vector Vaxzevria, recombinant protein Nuvaxovid, mRNA vaccines Spikevax and Comirnaty). Different study designs between trials. No safety concerns with coadministration, regardless of the type of COVID-19 vaccine and influenza vaccine administered. There was an absence of safety alerts in countries who implemented coadministration during 2021-22.	

Outcomes	Ref	Study type / Participants	Results	Findings
Other groups (not approved for use in NZ)				

Systematic review in adults >18 year-olds	[37]	SR of MF59 adjuvanted TIV compared with non-adjuvanted counterparts.	• SAE reported by 3 RCT and 2 NRSI (non-randomised studies of intervention) – GBS was seen in both aTIV (including one death) and non-a TIV studies.
			• Systemic AE in all adults and similar in older adults
			  ○ Combined systemic reactions: RR 1.18 (1.02-1.38, 5RCT, moderate certainty)
			  ○ Myalgia: RR 1.71 (1.09-2.69, 10 RCT, moderate)
			  ○ Fever: RR 1.97 (1.07-3.61, 9 RCT, low certainty)
			  ○ Chills: RR 1.70 (1.20-2.40, 7 RCT, moderate)
			• Local pain was more frequent in the aTIV groups (RR 2.02, 1.53-2.67, 12 RCT, moderate certainty) No difference for redness, swelling or induration.
			• No difference was seen in rate of hospitalisation for AEFI in either group
				Adjuvanted influenza vaccine is associated with a higher frequency local AE and systemic reactions compared with standard influenza vaccine.

Safety in at risk groups	[37]		Six studies inc HIV, HSCT and solid organ transplant recipients, institutionalised older adults and receiving regular medical care • Local reactions more common in aTIV groups receiving regular medical care • No difference in systemic AE for any group between aTIV and standard TIV • Shivers and fever more common in those with HIV.	No safety concerns were identified around the use of adjuvanted influenza vaccine in immunocompromised adults or those receiving regular medical care.
Cell-derived adjuvanted QIV in adults aged ≥50 years	[49]	Phase 2 RCT, 471 adults aged ≥50 years, cell-based aQIV compared with non-adjuvanted QIVc, recombinant (RIV4) and egg-based aQIV, proof-of-concept	Local solicited AE were reported at a similar rates by participants who receive adjuvanted vaccines which were higher than for non-adjuvanted vaccine. Majority of solicited AE was mild to moderate in all vaccine groups. aQIVc had higher rates of severe systemic solicited AE: • aQIVc (6/59 (5.2%) vs QIVc 3/31 (1.7%), aQIVe 2/57 (1.8%) and 3/64 (2.52%) RIV4 • Most frequent SAE were headache (n=4), loss of appetite (n=2) and 1 of each – nausea, fatigue, myalgia, arthralgia and chills. Generally lasted <7 days. • In aQIVc group – 1 case of GBS 39d post vaccination (assessed to be due to COVID-19 infection not vaccine related); 1 death (worsening congestive heart failure, not vaccine related)	Overall, the safety profile of cell-based adjuvanted influenza vaccine in those aged ≥50 years was acceptable with no identified safety concerns.

Outcomes	Ref	Study type / Participants	Results	Findings
Solid organ transplant patients adjuvant or HD	[48]	STOP-FLU trial, Swiss/Spanish RCT, 1:1:1 comparison aTIV (n=209), hd-TIV (n=203) and standard TIV (n=204). 2018/19 and 2019/20 season. age ≥18 patients (median 58 years) who underwent solid organ transplant at least 3 months prior to enrolment (excl ongoing anti-rejection therapy, immunoglobulins, eculizumab/rituximab within 6m, ABO incompatible transplant, pregnant/breastfeeding).	• Solicited AE – most mild and self-limiting: ○ 121/204 (59%) standard IIV ○ 177/209 (84%) aTIV ○ 175/203 (86%) hd-TIV • 1 SAE considered associated with vaccine – panniculitis 3 days after hd-TIV ○ Rates of anti-HLA antibodies and biopsy-proven rejection were low in all groups. ○ Two deaths not associated with vaccine or influenza	All three vaccines were safe and well tolerated in recipients of solid organ transplants.
Immunogenicity				
Older adults				
Comparison with IIV	[42]	SR – 49 RCTs comparing squalene-adjuvanted vs non-adjuvanted IIV, published 1999-2017. Trials conducted across all age groups. (young children and older adults predominantly, on one study in adolescents)	• Most cases the amount of HA was the same in both vaccines (total of 60µg), but where they differed, for example for dose sparing approaches, then adjuvanted IIV contained less HA than the corresponding non-adjuvanted vaccine. • The difference between pre- and post-vaccination GMT values decreased with higher pre-GMT values. • With increasing age, non-adjuvanted vaccine had a stronger effect on GMT than adjuvanted vaccine (converged at high age). Adjuvant effect is associated with preseason immunity measures. • Non-inferiority was demonstrated regardless of age. Superiority was predominantly seen in children (90% of comparisons in young children vs 9% in older adults).	This meta-analysis did not support the claim that squalene-based adjuvanted IIV was superior to standard aqueous IIV in older people with prior influenza immunity. This meta-analysis found that the additional benefit of adjuvant in influenza vaccines over standard influenza vaccine was greatest in young children and decreased with increasing age. The extent of the adjuvant effect was associated with preseason immunity.
Clinical relevance of increased antibody titres	[43]	A review of 3 meta-analyses and one trial comparing immunogenicity of adjuvanted and non-adjuvanted IIV.	• Agreement that to show adjuvant effect GMTR up to 1.5 if statistically significant on the 5% level. But are inconsistent as to whether effect sizes of up to 1.5 is clinically relevant to consider adjuvant superior to aqueous. • When compared with comparisons of TIV and QIV, which have GMTR of nearer 1 and upper 95% CI is 1.5 • Squalene-adjuvant may play a greater role in immunity than is detected by antibody and HAI assay titres. • When comparing adjuvant effect in other age groups, there could be an uptick in immunogenicity in immunosenescent older adults (which was more marked in a mouse model without prior influenza experience).	Available evidence shows that on average, squalene-adjuvanted influenza vaccine induces 1.5-fold higher antibody titres in older people than standard aqueous flu vaccine. The clinical relevance is not yet determined. But evidence shows that any influenza vaccine is better than none in older adults, irrespective of the type.

Outcomes	Ref	Study type / Participants	Results	Findings
Meta-analysis of RCTs in adults ≥65 years	[44]	Meta-analysis of RCTs of aTIV (phase 1-3, authors from Seqirus and Novartis) Total approx. 28300 participants from 58 studies during 1992-2013. Immunogenicity (HAI assay) data available for 27,116 participants aged ≥65 years. Full set analysis uniform definition was applied.	• Full set analysis – 11,105 participants (5869 aTIV and 5236 TIV). • The immunogenicity of the first dose (homologous strains): ○ Difference in seroconversion rates met noninferiority criteria aTIV vs TIV (lower 95% CI noninferior > -10% to statistical > 0): A/H3N2 10% (95% CI 6.6-14.5) A/H1N1 9.5% (5.2-13.9) B 12.7% (8.6-16.8) ○ GMTR (non-inferior lower 95% CI >0.67, statistical significance >1): A/H3N2 1.3 (95% CI 1.18-1.44) A/H1N1 1.15 (1.01 – 1.31) B 1.23 (1.15-1.31) ○ Differences in % with HAI titre ≥40: A/H3N2 2.7% (95% CI 0.9-4.5) A/H1N1 2.4% (0.8-4.0) B 4.5% (1.8-7.1) ○ Persistence of immunity to day 181 GMTR A/H3N2 1.11 (95% CI 1.02-1.21) A/H1N1 1.00 (0.89 – 1.12) B 1.08 (1.01-1.16)	Adjuvanted TIV elicited statistically higher haemagglutinin inhibiting antibody response compared with standard TIV in older adults, in the breadth and duration of the immune response for all the vaccine influenza strains, including for A/H3N2.
Comparison of aTIV and hd-TIV in long term care residents	[45]	Phase 4 active control trial. Volunteers received either aTIV (n=194) or hd-TIV (n=193) over 2018/19 and 2019/20 seasons. Aged 65-100 years living in long-term care facilities in Ohio, US. Samples taken d0 (-7 to 0), d28 (24-29), d180 (192-215, for 2018/19 season). Trial NCT03694808	• HAI GMTR hd-TIV : aTIV (based on 95% CI) ○ aTIV met non inferiority for A/H1N1 and A/H3N2 but not for B at D28. ○ A/H1N1 = 1.03 (0.76-1.4) ○ A/H3N2 = 1.04 (0.73-1.48) ○ B = 1.21 (0.81 – 1.61) • Seroconversion rates – non-inferiority not met for aTIV ○ H1N1: aTIV 39.6%, hd-TIV 43.7% ○ H3N2: aTIV 54.1% %, hd-TIV 64.2% ○ B: aTIV 35.6%, hd-TIV 43.0% • For both vaccines, over 80% Seroprotection for all strains when combined both seasons (HAI titre ≥40) • Anti-N Ab NI titre seroconversion rate – aTIV non-inferior to hd-TIV ○ H1N1 – aTIV 62%, hd-TIV 29%; NI GMTR 0.45 (0.33-0.63) ○ H3N2 – aTIV 27%, hd-TIV 16%; NI GMTR 0.95 (0.76-1.17)	Both vaccines induced a strong humoral response in older adults. Immunogenicity data favoured hd-TIV for HAI titre seroconversion but aTIV for anti-N antibody titres (NI titre). Suggests potential relevance for anti-neuraminidase response in protection. However, recombinant vaccines only contain HA not NA. Neuraminidase response is likely to be complementary but independent of haemagglutinin response.

Outcomes	Ref	Study type / Participants	Results	Findings
Comparative immunogenicity enhanced IIV	[46]	RCT, community-dwelling adults aged 65-82 years in Hong Kong (Oct 2017-Jan 2018). Comparing QIV, aTIV, hd-TIV, RIV4.	• In the assays, A/H1N1 and A/H3N2 strains were egg-propagated for HAI and micro-neutralisation (MN) assay used cell-propagated A/H3N2. • At 30 days post vaccination, mean fold rise in HAI titres and MN were significantly higher in all groups over standard vaccine. • MFR in MN assay: Recombinant (4.7-fold) > hd-QIV (3.4) and aQIV (2.9) vs standard QIV (2.3-fold). • Proportion with >4-fold rise to HAI titres ≥1:40 were statistically higher for all 3 enhanced vaccines: ○ A/H1N1 RIV4 60% (53-67%), hd-TIV 59% (52-66%), aQIV 60% (43.-67%) vs 42% (36-50) for QIV ○ A/H3N2 RIV4 56% (48-63%), hd-TIV 54% (46-61%), aQIV 48% (40-55%) vs 41% (34-48%) for QIV ○ B Victoria: RIV4 44% (34-51%), hd-TIV 52% (45-60%), aQIV 44% (37-51%) vs 48% (41-56%) for QIV • Boosting of IFN-γ CD8+ T cell responses also observed with enhanced vaccines, particularly to B/Victoria in which there was no significant rises for standard QIV • Antibody responses to cell-propagated a/H3N2 using MN were significantly higher for the RIV than the other vaccines.	This study found that all of the enhanced influenza vaccines had improved immunogenicity compared with standard QIV for A/H3N2 and A/H1N1 influenza in older adults. Recombinant QIV induced particularly high antibody response to the cell-like H3N2 strain. This study could not extrapolate immunogenicity to effectiveness.
Coadministration with RSV vaccine	[40]	Phase 3 RCT, open-label, in EU and UK. Adjuvanted RSVpreF (Arexvy) and aQIV coadministered or sequential admin (aQIV then RSV, 1 month apart) 1045 participants aged ≥65 years (mean age 72 years)	• Non-inferiority of aQIV and RSV coadmin vs sequential • HAI GMTR (upper 95% CI ≤1.5 seq:coad) ○ H1N1 1.04 (0.91-1.18) ○ H3N2 1.32 (1.13-1.53) – not non-inferior [MN GMTR post-hoc 1.23 (1.06-1.42)] ○ B/Victoria 0.97 (0.90-1.06) ○ B/Yama 1.04 (0.95-1.13) ○ A/Darwin(H3N2) which had low pre and post-GMTs for both groups which may have impacted GMTR calculations • RSV neutralisation GMTR ○ RSV-A 0.99 (0.87-1.12) ○ RSV-B 1.16 (1.03-1.30)	No clinically relevant interference of the immune responses to either vaccine. Non-inferiority was shown against A/H1N1 and B strains and marginally missed for A/Darwin(H3N2) which had low pre and post-GMTs (which may have impacted GMTR)
Coadministration with mRNA COVID-19 vaccine	[41]	SR conducted April 2022, 5 studies. 3 clinical trials compared safety and immunogenicity of coadministration with separate admin.	• BNT162b2 (Comirnaty) GMTR (coad vs monoadmin) ○ Age ≥65 years, aTIV ranged from 1.0 (0.86-1.15) for B/Yama) to 1.18 (1.02-1.37) for H3N2 ○	No immune interference were found with coadministration regardless of which influenza vaccine or COVID-19 vaccine were given or by age (< 65 or >65)

Outcomes	Ref	Study type / Participants	Results	Findings
Other groups				
Patients with HIV	47	SR of 11 studies (4 RCT, 2 cohort, 5 self-controlled), adjuvanted IIV in patients with HIV infection.	Meta-analysis found, generally, the results of GMT, seroconversion and seroprotection rates indicated that adjuvanted influenza vaccination in patients infected with HIV could improve the immunogenicity. Identified a lack a comparison between healthy and HIV-infected groups	
Solid organ trans plant patients adjuvant or HD	48	STOP-FLU trial, Swiss/Spanish RCT, 1:1:1 comparison aTIV (n=209), hd-TIV (n=203) and standard TIV (n=204). 2018/19 and 2019/20 season. age ≥18 patients (median 58 years) who underwent solid organ transplant at least 3 months prior to enrolment (excl ongoing anti-rejection therapy, immunoglobulins, eculizumab/rituximab within 6m, ABO incompatible transplant, pregnant/breastfeeding).	• Seroconversion- ≥4-fold increase in HAI above baseline • Seroprotection HAI titre ≥40 • Response rate ○ 84/198 (42%) TIV, 122/205 (60%) aTIV, 129/195 (66%) hd-TIV ○ Difference aTIV vs TIV = 0.17 (95% CI 0.08-1, p<0.001); hd-TIV vs TIV = 0.24 (97.5% CI 0.16-1, p<0.001); no difference between hd-TIV and aTIV = 0.07 (95% CI -0.01 to 1, p=0.085) • Seroconversion rates – higher in intervention than control group (range 25% - 57% vs 13% -35%, depending on vaccine strain). • Seroprotection rates were higher on day 28. • No difference between groups in incidence of confirmed influenza infection (35/598, 6%) participants. ○ 66% of these were detected only by systematic nasopharyngeal surveillance.	Study showed improved humoral immunity against influenza with adjuvanted or high dose IIV compared with standard influenza vaccine in solid organ transplant recipients.
Cell-derived adjuvanted QIV in adults aged ≥50 years	49	Phase 2 RCT, 471 adults mean age 65 years (range 50-87), cell-based aQIV compared with non-adjuvanted QIVc, recombinant QIV and egg-based aQIV, proof-of-concept (Seqirus)	Immunogenicity assessed in 449 participants at d29 and 441 at day 181 71.8% had been previously vaccinated within last 3 years. Comparison of GMT ratios against each influenza strain (HAI against cell-based strains) Estimated GMTR favoured cell-based aQIV for age subgroups and overall population, and were higher for ≥65y for A/H1N1, A/H3N2 and B/Vic strains. Compared with hd-QIV, cell-aQIV had a lower response to A strains and higher against B. Compared with egg-aQIV, cell-aQIV produced higher immune response when using cell-based strains in HAI assay.	Data suggest that MF59 adjuvant enhances QIVc immune response against haemagglutinin and neuraminidase for all four strains. Adjuvant did not enhance the breadth of the response to heterologous strains, and persistence at day 181. Formulations with both higher antigen level and adjuvant may be needed to induce a broader and more sustained response.
Effectiveness				

Outcomes	Ref	Study type / Participants	Results	Findings
Mismatched season	[50]	Phase 3 RCT (Seqirus), 89 sites 12 countries 2016/17 northern and 2017 southern seasons. Community dwelling adults ≥65 +/- comorbidities. Stratified by age 65-74 and ≥75, and by risk of influenza complications (high or low) Randomised to aQIV or Tdap	• Primary outcome – RT-PCR confirmed influenza from day 21-180 (or end of flu season). o aQIV – 122 influenza cases (3.6%) / 3381 o Tdap – 151 (4.5%) influenza cases / 3380 o Majority – A/H3N2, 85% isolates mismatched to vaccine strain o VE 19.8% (-5.3 to 38.9) against all ILI influenza and 49.9% (-24.0 to 79.8) against antigenically matched strains PCR confirmed ILI criteria: • Protocol - respiratory and systemic symptoms (not necessarily including fever); modified CDC ILI – presence of low-grade fever (>37.2°C) sore throat and/or cough; WHO ILI (in post-hoc analysis) fever ≥38°C and cough. • Efficacy against any PCR confirmed protocol ILI = 19.8% (-5.3 to 38.9) vs WHO ILI = 51.1% (28.2-66.7%).	Prespecified efficacy criteria was not met for aQIV in older adults during seasons with predominant A/H3N2 with a high degree vaccine strain of mismatch. VE was higher against influenza with more clinically significant disease.
Systematic review European perspective	[51]	SR (Seqirus funded) 11 analyses from 9 real-world evidence studies, with 53 million participants aged ≥65 years during flu seasons in 2006-2009 and 2011-2020.	• 9 analyses found aTIV more effective than standard TIV or QIV in reducing influenza-related outcomes. o aTIV vs TIV range rVE 7.5 – 25.6%; aTIV vs QIV range rVE 7.1 –36.3% • 7 analyses found similar effectiveness aTIV vs hd-TIV • 3 analyses found aTIV > hd-TIV (IRME range 6.6% - 16.6%) • Risk of bias was moderate to high.	Both adjuvanted and high-dose influenza vaccines are effective for vaccination programmes in older adults and preferred over standard-dose influenza vaccines.
Comparative effectiveness adjuvanted TIV vs non-adjuvant QIV	[52]	SR (Seqirus funded) 16/21 studies used for meta-analysis Many of the studies were conducted over 2017/18 season, 2 studies over 2018/19, comparisons with TIV were earlier.	Pooled VE estimate aTIV • Medical encounters due to lab-confirmed influenza o Outpatient visits 40.7% (21.9-54.9, I^2 = 0%, 4 studies) o Hospitalisation 58.5% (40.7-70.9, I^2 = 52.9%, 3 studies) o Influenza/pneumonia hospitalisation = 51.3% (39.1-61.1, I^2=0, 4 studies) • Relative VE aTIV vs TIV and QIV o 13.9% (4.2 – 23.5, I2 =95.9%. 8 studies) and 13.7 (3.1-24.2 I^2 =98.8%, 7 studies) • rVE aTIV vs hd-TIV 2.8 (-2.9 – 8.5; I^2= 94.5%. 7 studies) • three cohort studies in the US during 2017/18 reported different results when comparing aTIV with other vaccines in older adults, using different databases.	aTIV was more effective than standard QIV at preventing laboratory-confirmed influenza and IRME, and was comparable to hd-TIV.

Outcomes	Ref	Study type / Participants	Results	Findings
Relative effectiveness aTIV to standard QIV	[53]	Retrospective cohort study (Seqirus) 2019/2020 season in US. electronic health records, primary care and specialist clinics linked to pharmacy and medical claims data. Outcomes: influenza related medical encounters (IRMEs), outpatient IRMEs, and influenza- and pneumonia-related (I/P) hospitalisation Population(total >3.5 million adults aged ≥65): aTIV=936,507 and TIV=651,034; (hd-TIV=1,813,819 recipients) A/H1N1 was predominant strain in older population (73% of circulating virus) Note – this season overlapped with the start of the COVID-19 pandemic.	• Of cohort – 26.4% aTIV, 18.3% standard QIV (plus 4.3% received standard TIV) and 51.0% hd-TIV • Mean age approx. 75 +/- 7 years. • Similar incidence of comorbidity between groups (Charlson comorbidity index aTIV 1.4 ±1.8; QIV 1.7 ± 2.0, hd-TIV 1.6 ± 1.9 – measures burden of comorbid conditions of mortality and adverse health outcomes) [aTIV – baseline fewer outpatient and inpatient visits] • Most common medical conditions were comparable across the groups (chronic pulmonary disease, diabetes, renal disease and peripheral vascular disease) • Any IRME – 0.5% aTIV , QIV 0.9%, hd-TIV 0.7% • Relative VE (aTIV vs QIV)	This study concluded that aTIV was more effective than standard QIV or hd-TIV at preventing IRME in older adults during the 2019/2020 US influenza season. When influenza was the admitting diagnosis, inpatient relative VE was not statistically different between aTIV and hd-TIV.

Adults with risk factors	[54]	Retrospective study as above (Seqirus)
		Cohort: ~1.67 million adults aged ≥65 years (mean 74.9±6.2 aTIV, 74.0± SD 6.7 QIV) with ≥1 high-risk condition
		Antigenically drifted A/H1N1pdm09 and B/Vic resulted in a lower absolute VE (~30%)
			• 57% cohort received aTIV and 43% standard QIV.
			• Top 3 comorbidities – heart disease, metabolic disorders, endocrine disorders
			• After IPTW:
			  ○ Any IRME – 0.7% aTIV vs 0.9% QIV
			  ○ Outpatient IRME = 0.6% vs 0.8%
			  ○ Influenza/pneumonia hospitalisation = 0.8% vs 1.0%
			• Relative VE (aTIV vs QIV)
			  ○ Any IRME = 23.6% (95% CI 20.9-26.1)
			  ○ Outpatient IRME = 23.3% (20.4-26.1)
			  ○ I/P hospitalisation = 19.0 (16.3-21.6)
			• rEV for specific high risk conditions
			  ○ Any IRME = aTIV > QIV for all, except BMI ≥40 (wide error bars)
			  ○ Outpatient IRME = aTIV > QIV for all except BMI≥40 and stroke
			  ○ I/P hospitalisation = aTIV > QIV for all except BMI ≥40
			• Post-hoc analysis rVE ≥1 high risk condition AND BMI ≥30
			  aTIV > QIV for all outcomes
			  ○ Any IRME = 22.4% (95% CI 16.2-28.1)
			  ○ Outpatient IRME = 22.5% (15.8-28.7)
			  ○ I/P hospitalisation = 14.0 (7.0-20.5)
				aTIV was more effective than QIV in adults aged ≥65 years with at least one high-risk condition against any IRME, outpatient IRME and influenza- or pneumonia-related hospitalisation.
				During the season of study, both vaccines had reduced effectiveness against A/H1N1 and B/Victoria influenza due to antigenic drift in the wild-type virus strains
				.

Outcomes	Ref	Study type / Participants	Results	Findings

Cardiorespiratory hospitalisation	[55]	Retrospective study as above (Seqirus)
		4.3 million adults aged ≥65 years who received aTIV , hd-QIV or QIV during 2019/2020 season
			• Relative VE cardiorespiratory hospital diagnoses (incl respiratory infections, myocardial infarction, ischaemic stroke)
			  ○ aTIV vs hd-TIV = 3.9% (2.7-5.0)
			  ○ aTIV vs QIV = 9.0% (7.7-10.4)
			• rVE Influenza hospitalisation
			  ○ aTIV vs hd-TIV = 9.7% (1.9-17.0)
			  ○ aTIV vs QIV = 25.3% (17.7-32.2)
				Fewer cardiorespiratory hospitalisation (virus respiratory infections overall, influenza, pneumonia, MI) were seen in adults aged ≥65 years vaccinated with aTIV during 2019-2020 influenza season than those vaccinated with hd-TIV or QIV. Also observed fewer hospitalisation for ischaemic stroke in those who received aTIV than QIV.

Frail adults	[56]	Test negative, pooled data from CIRN SOS network 2012-2015 flu seasons – with clinical frailty scale (CFS) data. A/H3N2 was most type, but a large proportion of influenza A samples were untyped Vaccination type was not randomised.	3441 cases and 3660 controls, aged ≥65 years Most of those immunised had received standard TIV (85.6%), 526 received aTIV. Frailty was highest among those who received aTIV. • severely frail 33.3% aTIV vs 5.6% TIV • Non-frail 55.4% TIV and 15.2% aTIV 1578 (45.9%) flu+ were immunised in that season vs 2312 (63.2%) of flu neg controls. VE (IPTW) against hospitalisation for lab-confirmed influenza (before adjusting for frailty • Standard TIV 45.9% (40.2-50.1) • aTIV – 53.5% (42.8-62.3) • No significant difference by sex, age, or influenza season. Trend favouring aTIV. • aTIV had higher VE against A/H1N1pdm09, lower VE for a/H3N2 than standard TIV (compromised due to untyped virus) VE (IPTW) against hospitalisation for lab-confirmed influenza (adjusting for frailty • aTIV – 59.1% (49.6-66.8) • TIV – 44.8% (39.1-50.0) • rVE lab-confirmed influenza 25% (OR 0.75, 0.61-0.92) – favouring aTIV	Both TIV and aTIV are effective against influenza-related hospitalisation (VE range 45-54%). Overall, no significant difference between the vaccines. Taking frailty into consideration, VE estimates remained similar for standard TIV and higher for aTIV. Relative VE against laboratory-confirmed influenza indicated that aTIV was around 25% more effective than TIV. The higher effectiveness for aTIV appeared most against a/H1N1 Albeit with a small sample size, the data suggested that aTIV was more effective in adults aged ≥85 years.
Comparison adjuvant with high dose influenza vaccine	[57]	SR of 10 studies Moderate risk of bias.	No head-to-head RCT studies found, 10 studies were retrospective cohort studies in US elderly. No studies had laboratory confirmed influenza as an endpoint. Most pooled relative effectiveness estimates were close to null.	Adjuvanted and high dose vaccines appeared to have similar effectiveness against influenza in older adults. No preference could be drawn to recommend one over the other.

Outcomes	Ref	Study type / Participants	Results	Findings
Impact effectiveness, comparison with standard QIV	[58]	Denmark, 2024/25 influenza season. comparison aQIV, QIV and hd-QIV aged≥65 years. Age ≥70 offered aQIV, 65-69 offered QIV and subset in study aged ≥65 years randomised to hd-QIV or standard A/H1N1pdm09 predominant (53% subtyped cases, and 60% of cases in this study) with considerable A/H3N2 cocirculation (47% submitted samples) Routine guidelines – all patients belonging to risk groups including ≥65 years presenting with ILI to GP or with ILI+LRT symptoms at hospital be PCR tested for influenza A and B.	A/H1N1pdm09 predominant (53% subtyped cases, and 60% of cases in this study) with considerable A/H3N2 cocirculation (47% submitted samples) Among 20,615 vaccinated people aged ≥65 years: 73.7% received aQIV; 19.5% standard QIV and 6.8% hd-QIV. Of 3,340 influenza A cases, 42% (1403) were non-hospitalised. More with chronic conditions were hospitlised (76.1% vs 56.7% non-hospitalised). More non-hospitalised vaccinated influenza A cases (68.8%) and controls (69.7%) than the vaccinated hospitalised cases (60.3%) vs controls (59.0%) Overall VE estimates (hospitalised and non-hospitalised cases, p-values compared with QIV): QIV 33% (24-41) • aQIV 48% (42-52; p<0.0001) • hd-QIV 50% (38-59%) – similar to aQIV (note aQIV only given to those aged ≥70 years) VE hospitalised • QIV – 26% (23-47) • aQIV – 47% (41-53, p=0.001) • hd-QIV – 53 (35-66, p=0.05	The introduction of aQIV significantly improve influenza protection in adults aged ≥65 year, and specifically age ≥70 years. Similar effectiveness was shown between aQIV and hd-QIV. These vaccines provide enhanced benefit in reducing severe influenza outcomes in older adults.
Comparison aTIV and hd-TIV	[59]	Retrospective test-neg design study in US adults ages ≥65 years over 3 season 2017-2020. Visit to ED or inpatient with acute respiratory or febrile illness, tested for influenza	Pooled analysis over three seasons, rVE: • test-confirmed influenza in ED/inpatient = -2.5% (-19.6 to 12.2) • hospital admission alone = -1.6 (-22.5 to 15.7) • no significant difference between seasons	Effectiveness of aTIV and hd-TIV against test-confirmed influenza hospital visit or admission was comparable in the US in older adults aged ≥65 years.
Lab-confirmed influenza-associated SARI	[104]	Italian, 512 vaccinated SARI patients – 83 influenza cases and 429 test negative controls. Most registered in 2018/2019 season – influenza A predominant. Baseline characteristics of those who received aTIV or QIV differed (used propensity score matching)	• aTIV was more frequent among cases than controls • Across both seasons 53% of cases were A/H3N2 • rVE (aTIV vs QIV) against any influenza was 59.2% (16.6-80.5%, p=0.0017) • Point estimates in rVE (aTIV vs QIV) were very similar for A/H1N1 (5 and A/H3N2 protection	In two seasons with predominant influenza A infections and with a high proportion of A/H3N2 mismatching, aTIV was more effective than QIV in preventing laboratory-confirmed influenza SARI among hospitalised older adults.

Abbreviations: AE – adverse events; AEFI – adverse events following immunisation; 95% CI – 95% confidence interval; aQIV – adjuvanted quadrivalent influenza vaccine; aTIV – adjuvanted trivalent influenza vaccine EMR – electronic medical records; GB – Great Britain; GI – gastrointestinal; HA – haemagglutinin; HAI – haemagglutinin inhibition assay; hd-TIV – high-dose trivalent influenza vaccine; IFN – interferon; IPTW - inverse probability of treatment weighting; IRME – influenza-related medical encounter; KPSC – Kaise Permanente Southern California; LAIV – live attenuated influenza vaccine; m – months; MFR – mean fold rise; MN - micro-neutralisation assay QIV – quadrivalent influenza vaccine; RCT – randomised controlled trial; rVE – relative vaccine efficacy/effectiveness; SAE – serious adverse events; SR – systematic review; TIV – trivalent influenza vaccine; US – United States [of America]; VE – vaccine efficacy/effectiveness; vs – versus; y - years

Table 10: High-dose influenza vaccine

Outcomes	Ref	Study type / Participants	Results	Findings
Safety				

Comparison with standard dose	[60]	Phase 3 RCT in Europe (NCT04024228), with 1,528 participants aged ≥60 years (mean age 67, range 60-93) randomised to QIV or hd-QIV during 2019/20 season. (dose 0.5ml vs 0.7ml, 15µg vs 60µg of HA per strain)
		Reactogenicity 7 days, SAE and AESI – 28 days up to 180 days.
			Most frequently reported reaction was injection-site pain:
			• ages 60-64y = 51.7% hd-QIV vs 23.6% QIV
			• ages ≥65 years = 39.4 hd-QIV vs 18.3% QIV
			• Most started and resolved within 3 days and of mild to moderate intensity
			• Grade 3 injection site reactions (most common erythema): hd-QIV 7 (1.8%) vs QIV 2 (0.5%)
			Most frequent solicited systemic reactions were myalgia and headache, also reported malaise and shivering:
			• Aged 60-64 years
			  ○ Myalgia – 31% hd-QIV
			  ○ Headache – 30.2% hd-QIV vs 19.9% QIV
			• Age ≥65 years
			  ○ Myalgia – 21.6% hd-QIV
			  ○ Headache – 17.3% QIV
			No SAE considered vaccine related or AESI occurred within 28 days of vaccination
				No major safety concerns were shown. High-dose QIV was well tolerated. Safety outcomes for high dose and standard dose QIV were similar in both age groups, except that as expected, more solicited reactions were reported with hd-QIV than QIV in those aged 60-64 years.

GBS risk	[61]	VSD study, 2018/19 days 1-42 after hd-TIV ageas ≥65 years (median age 73 years, IQR 69-79). Control window 43-84 days post vaccination.	• Risk window 8-21 days – OR 1.85 (0.99-3.44) • 1-42 days – OR 1.30 (0.78-2.18) • Days 1-42, vaccinated with hd-QIV early in season (80%) - attributable risk/million vaccinations = 0.76 (-1.20 to 2.56) ○ Comparable to all influenza vaccines – AR 0.58 (-0.92-2.00) / million doses • Chart-confirmed rapid cycle analysis - 1 case GBS each in risk and control windows after 646,996 vaccinations. RR 1.0 (0.06-15.99)	Analysis of just under 650,000 vaccinations with hd-TIV no statistically significant signal for increased risk of Guillain-Barré syndrome in adults aged ≥65 years.

Outcomes	Ref	Study type / Participants	Results	Findings
Coadministration with recombinant zoster vaccine (rZV)	[39]	RCT, blinded conducted during 2021/22 and 2022/23 influenza seasons in US among 271 community-dwelling adults aged ≥65 years (median age 71 years, range 65-92), comparison of aQIV or hd-QIV with rZV.	• 137 received hd-QIV with rZV • Also non-inferior difference between groups after 2nd dose RZV alone. • Clinically similar patterns of SAE among ages 65-70 y and >70 years • During 43-day follow-up period, there were not cases of GBS or deaths. • 1 SAE – left partial cranial nerve III palsy occurring 25 days post-vaccination, was possibly related to RZV and hd-QIV. Completely resolved by 8 weeks	No significant difference between groups. Study supports safety for coadministration of hd-QIV and rZV among older adults.
Immunogenicity				
Comparative immunogenicity	[62]	SR (WHO/CDC) 7 trials incl hd-IIV vs sd-IIV 10492 adults ≥60 for Article to 2017 Three outcomes – MFR (high heterogeneity), GMTR, difference in elevated titres. Compared with adjuvanted and intradermal vaccines.	• High dose vaccines – 82% (73-91%) higher post vaccination HAI titres to A/H3N2 than standard. • Significantly higher GMT than adjuvanted and intradermal IIV against A/H1N1 and B/Vic • Pooled estimate absolute difference in participants with post vaccination titres ≥40 hd vs sd ○ A/H1N1 = 8.0 % (5.2-11.0%, 8 studies, I^2 88%) ○ A/H3N2 = 3.0% (2.2-3.8%, 8 studies, I^2 39%) B/Vic = 10.4 % (7.7-13.2, 5 studies, I^2 66%)	Found comparable immunogenicity profiles among enhanced influenza vaccines, based on HAI titres. HD elicited higher post vaccination GMT against A/H3N2 than standard vaccine and against A/H1N1 and B/Vic than other enhanced vaccines. All of the enhance vaccines induced greater immune response than standard vaccine. Study limited to reviewing HAI titres and not the broader immune response. Head-to-head studies conducted over multiple seasons would be informative.
Comparison with standard dose	[60]	Phase 3 RCT in Europe (NCT04024228), with 1,528 participants aged ≥60 years (mean age 67, range 60-93) randomised to QIV or hd-QIV during 2019/20 season. (Dose 0.5ml vs 0.7ml, 15µg vs 60µg of HA per strain). GMT compared for each strain with SD vaccine	• Aged 60-64, n=379 hd-QIV and 381 sd-QIV and age ≥65y, n=395 vs 384 • GMTRs in HAI for each strain, more participants in hd than sd achieved ≥40 titre, slightly higher for younger group. • Neutralising Ab (SN assay) - highest for 60-64 – lowest for A/H3N2; 99-100% had titres ≥1:10, similar between groups. • Seroconversion rates at day 28 were lower for those with no history of influenza vaccination than those who had been vaccinated in the previous year, consistent between groups. • Baseline and post vaccination GMT and seroconversion rates were similar between participant with and without at-risk conditions in both age groups.	hd-QIV had superior immunogenicity to all four virus strains than standard vaccine. The immune response was robust irrespective of prior influenza vaccine history or underlying medical conditions that are associated with influenza-related complications
Special groups				

Outcomes	Ref	Study type / Participants	Results	Findings

Solid organ trans plant patients adjuvant or HD	[48]	STOP-FLU trial, Swiss/Spanish
		RCT, 1:1:1 comparison aTIV (n=209), hd-TIV (n=203) and standard TIV (n=204). 2018/19 and 2019/20 season. age ≥18 patients (median 58 years) who underwent solid organ transplant at least 3 months prior to enrolment (excl ongoing anti-rejection therapy, immunoglobulins, eculizumab/rituximab within 6m, ABO incompatible transplant, pregnant/breastfeeding).
			• Seroconversion- ≥4-fold increase in HAI above baseline
			• Seroprotection HAI titre ≥40
			• Response rate
			  ○ 84/198 (42%) TIV, 129/195 (66%) hd-TIV
			  ○ Difference hd-TIV vs TIV = 0.24 (97.5% CI 0.16-1, p<0.001); no difference between hd-TIV and aTIV = 0.07 (95% CI -0.01 to 1, p=0.085)
			• Seroconversion rates – higher in intervention than control group (range 25% - 57% vs 13% -35%, depending on vaccine strain).
			• Seroprotection rates were higher on day 28.
			• No difference between groups in incidence of confirmed influenza infection (35/598, 6%) participants.
			  ○ 66% of these were detected only by systematic nasopharyngeal surveillance.
				Study showed improved humoral immunity against influenza with adjuvanted or high dose IIV compared with standard influenza vaccine in solid organ transplant recipients.

Inflammatory bowel disease on TNF mAb	[63]	Phase 4 RCT 40 patients aged 18-64 years with IBD on anti-TNF monotherapy and 19 on vedolizumab (HD or SD-TIV) and 20 healthy controls (SD vaccine), 2016/17 and 2017/18 seasons. Vedolizumab – blocks α4β7 integrin in gut, targets gut inflammation only	Group who received HD were younger than SD dose (29y vs 43y, p=0.004) More of HD group were treated with infliximab (64% vs 27%, p<0.05) No differences between vedolizumab and healthy control groups. • HD group had higher A/H3N2 Ab than SD (patients and controls), not diff for A/H1N1 of B/Vic. • By 6 months post vaccination – antibody had waned more rapidly in HD group and no difference to SD groups. Patients on vedolizumab had similar responses to SD as controls at all time points.	High dose influenza vaccine induces higher antibody concentrations than standard dose vaccine in patients with IBD treated with anti-TNF therapies. Vedolizumab does not affect the immunogenicity of influenza vaccination in patients with IBD, with comparative responses to those seen in healthy controls.
HSCT	[64]	Phase 2 RCT in US – 2 doses hd-TIV vs 2 doses sd-TIV in patients aged ≥18 years, 3-23 months post-allogenic HSCT (doses 28-42 days apart). 60 hd-TIV and 64 sdQIV	Median age 57.8 years (IQR 42-64) Median time post transplant – 5.6 months, 57% received first dose <6 months post HSCT • Following 2nd dose, GMT HD > SD, aGMTR: ○ A/H3N2 2.09 (1.19-3.68) ○ B/Vic 1.61 (1.00-2.58) ○ Baseline titres predicted post dose 2 titres. ○ Higher titres for ≥1 Ag significantly associated with: hd-TIV, longer time post-HSCT, higher CD4+ and CD19+ cells and lower absolute lymphocyte counts • At 6 months post vaccine, GMFR resembled those after dose 1. • GMTR HD:SD A/H3N2= 1.87 (1.05-3.34); B/Vic = 1.63 (1.00-2.65)	Two doses of hd-TIV given at least 4 weeks apart was more immunogenic for A/H3N2 and B/Vic compared with SD-TIV, with higher GMTs at 1 month and 6 months after 2nd dose

Outcomes	Ref	Study type / Participants	Results	Findings
Leukaemia	[65]	Prospective pilot study 2013/14 and 2014/15 influenza seasons Mayo clinic US. 13 patients with monoclonal B cell lymphocytosis (MBL) and 17 untreated chronic lymphocytic leukaemia (CLL). Median age 69.5 years (49-82). Given HD-IIV	At baseline, total Ig and lymphocyte counts in MBL > CLL. Day 28 HAI GMTR d28:d0: • A/H1N1 – overall 2.8 (0.3-26.0), MBL=CLL • A/H3N2 – overall 4.4 (0.2-1 112) MBL >CLL (p=0.06) • B – overall 2.0 (0.1-28) MBL>CLL (p=0.02) Seroconversion: (a high proportion overall already had seroprotective Ab titres at baseline) • A/H1N1 = 10% overall • A/H3N2 = 21.7% • B = 10% (none of CLL group seroconverted vs 23% MBL) ELISPOT assay – MBL cohort had higher memory B cell results to each of 3 viruses than CLL. CLL group had virtually no memory response to influenza.	Unlike previous studies with standard influenza vaccine, this study demonstrated that most people with MBL and CLL developed influenza Seroprotection in response to high-dose TIV. This study supports the vaccination of people with MBL and CLL against influenza, even with suboptimal responses.
Effectiveness				

Comparison of enhanced influenza vaccines	[66]	ECDC SR hd-IIV vs standard
		36 studies, 2 RCT efficacy and 9 effectiveness.
			• 1 RCT data Relative efficacy hd vs sd against:
			  ○ laboratory-confirmed protocol defined ILI (VE 24.2%, 9.7-36.5) but not when modified CDC-defined ILI (VE 20.6, -4.6-39.9)
			  ○ Respiratory illness 18.3% (5-29.8)
			  ○ All cause hospitalisations 6.9% (0.5-12.8)
			  ○ Serious cardiorespiratory events 17.7% (6.6-27.4)
			  ○ Pneumonia events 39.8% (19.3-55.1)
			• The data was largely restricted to cohort studies.
			  ○ Influenza-related hospitalisation – fix effect rVE 13.5 (7.3-19.3)
				Limited data appeared to suggest that high dose influenza vaccines improved protection compared with standard dose or no vaccination in older adults.

Effectiveness by circulating strain and antigen match	[67]	SR/MA (Sanofi) – 15 publications over 10 consecutive flu seasons, >22 million received hd-TIV	All flu seasons - HD vs SD rVE • ILI = 15.9% (4.1-26.3) • All cause hospital admission – 8.4% (5.7-11.0) • Influenza hospital admission – 11.7% (7.0-16.1%) • Pneumonia – 27.3% (15.3-37.6) • Influenza/pneumonia – 13.4% (7.3-19.2%) • Mortality due to pneumonia/influenza = 39.9% (18.6-55.6%) • Similar for both matched and mismatched seasons and in seasons predominated with A/H3N2 or A/H1N1.	hd-TIV was consistently more effective than SD-TIV in adults aged ≥65 years in reducing influenza cases and influenza-associated complications, irrespective of the circulating strain and antigenic match.

Outcomes	Ref	Study type / Participants	Results	Findings
Mortality	[68]	Retrospective cohort study (Sanofi), US claims data 2016-2019 seasons. 44,456 influenza cases (52% unvaccinated, 33.8% HD, 14.2% SD) aged ≥65 years Seasons: • 2016/17 – 74% H3N2 (well matched), 3% H1N1, 23% B • 2017/18 – 60% H3N2 (poorly matched), 11% H1N1, 29% B • 2018-2019 42% H3N2, 52% H1N1, 6% B (2 waves, 1st H1N1, 2nd wave mismatched H3N2).	Mortality reduction • HD vs no vaccine – 17-29% • SD vs no vaccine = 25% in 2016/17 with good match between vaccine and circulating virus HD reduction in mortality seen but non-significant in 2 mismatch seasons • Vs no vaccine – IRR 0.83 (0.72-0.95) • Vs SD – IRR 0.83 (0.67-1.01)	High dose influenza vaccines significantly reduce the risk of mortality following influenza-related hospitalisation compared with those who are unvaccinated. In season, where vaccine matched circulating strain, comparable protection was provided by standard vaccine. In a season where there was a mismatch, HD vaccine was more protective and reduced mortality among breakthrough infections than SD.
Severe outcomes	[69]	Sanofi RCT DANFLU (NCT05517174) open label Denmark 2022-2025 332,438 participants randomised 1:1 to HD or SD IIV Median age 73.7 ± 5.8 years Primary endpoint – hospitalisation for influenza or pneumonia >14 after vaccination to 31 May of following year.	Primary endpoint: • Hospitalisation for influenza or pneumonia (n=1138 HD and 1,210 SD) 0.06% HD vs 0.11% SD = rVE 5.9% (-2.1 to 13.4, p=0.14) Secondary endpoints hospitalisation for : • Pneumonia (n= 1,045 vs 1,050) 0.63% vs 0.63%; rVE 0.5% (-8.6 to 8.3) • cardio-respiratory disease 2.25% vs 2.38% (rVE 5.7% (1.4-9.9) • any cause 9.38% vs 9.58% (rVE 2.1% (-0.1-4.3) • death any cause 0.67% vs 0.66% (rVE -2.5%, -11.6 to 5.9) • ICD-10 code influenza (without +ve test, n=101 vs 179) 0.06% vs 0.11% (rVE 43.6 % (27.5 to 53.6) Exploratory endpoint: • Influenza hospitalisation (lab-confirmed, before or within 3 days after hospitalisation but without specific influenza ICD-10 code, n=117 vs 276) 0.11% vs 0.17% rVE 35.9% (22.2-47.3) Subgroup analysis of the primary endpoint found in most cases with at least one co-morbidity, favoured HD, albeit with wide error margins.	High-dose IIV was not significantly different from standard dose IIV in reducing influenza or pneumonia hospitalisations. When the incidence of hospitalisations with ICD10 code influenza or lab-confirmed influenza was assessed, HD was more effective in preventing influenza than standard dose.

Outcomes	Ref	Study type / Participants	Results	Findings
Hospitalisations	[70]	Sanofi RCT GALFLU (NCT06141655) open label active-controlled study registry-based study in Spain (Galicia) 2023/24 and 24/25 seasons 103,169 community-dwelling participants aged 65-79 years (mean age 72.3 ± 4.3 years)	Primary endpoint (n=401 participants) • Hospitalisation for influenza or pneumonia absolute risk 0.26% HD vs 0.34% SD, rVE 23.7% 6.6-37.7 Secondary endpoints hospitalisation for: • Influenza (ICD-10, not confirmed, n=63 vs 92) 0.09% vs 0.14%, rVE 31.8% (5.0 to 51.3) • Pneumonia (n=116 vs 137) 0.17% vs 0.21%, rVE 15.7% (−8.7 to 34.8) • cardio-respiratory disease (n=985 vs 1071) 1.47% vs 1.60%, rVE 8.4% (0.1 to 16.1) • any cause (n=4336 s 4427) 6.46% vs 6.63%, rVE 2.5% (−1.7 to 6.5) • death any cause (n=305 vs 348) 0.45 vs 0.52, rVE 2.8 (−2.0 to 25.4) Exploratory endpoint • Influenza (lab-confirmed, not ICD-10) 0.11 vs 0.13, rVE 19.5 (−11.1 to 41.8)	Older adults who received HD vaccine were 24% less likely to be hospitalised with influenza (19.% less lab-confirmed influenza) or pneumonia than those who received SD influenza vaccine.

Abbreviations: AE – adverse events; AEFI – adverse events following immunisation; 95% CI – 95% confidence interval; CLL – chronic lymphocytic leukaemia; EMR – electronic medical records; GB – Great Britain; GI – gastrointestinal; GMTR – geometric mean titre ratio; HA – haemagglutinin; HAI – haemagglutinin inhibition assay; HD – high dose; hd-TIV – high-dose trivalent influenza vaccine; IBD – inflammatory bowel disease; IFN – interferon; IPTW - inverse probability of treatment weighting; ILI – influenza-like illness; IRME – influenza-related medical encounter; IRR – incidence rate ratio; KPSC – Kaise Permanente Southern California; LAIV – live attenuated influenza vaccine; m – months; MBL – monoclonal B cell lymphocytosis; MFR – mean fold rise; QIV – quadrivalent influenza vaccine; RCT – randomised controlled trial; rVE – relative vaccine efficacy/effectiveness; SAE – serious adverse events; SD – standard dose; SR – systematic review; TIV – trivalent influenza vaccine; US – United States [of America]; VE – vaccine efficacy/effectiveness; vs – versus; y - years

Table 11: Recombinant influenza vaccine

Outcomes/ group	Ref	Study type / Participants	Results	Findings
Safety				
Comparison with standard IIV	[71]	RCT adults aged 18-49 years, 998 received RIV4 and 332 standard QIV.	Participant recorded reactions within 7 days of vaccination • Similar frequency and severity between groups • Injection site pain and tenderness reported by around 50%, mild • Erythema <5% but more frequent in RIV4 than QIV (4.2% vs 0.9) • Systemic reactions – similar between groups, 34% RIV4 vs 36% QIV • Fever was rare, and no cases >40°C Unsolicited AE within 28 days – similar, no clinically concerning or unexpected. Most complaints were commonly associated with winter season. No vaccinated related SAE	Safety profile of recombinant influenza vaccine was like standard influenza vaccine. Vaccine was safe and well tolerated.
Systematic review aged >18 years	[72]	SR, published to Feb 2020, ten RCT studies.	Two SAE possibly related to RIV - vasovagal syncope and pericardial effusion. Local reactions – comparable with IIV RR 0.94 (0.9-0.98; 3 RCT) Systemic reactions – chills RR 1.33 (1.03-1.72, 3 RCT, low certainty). From 10 RCT no other significantly different comes. At risk populations – 6/ 27 patients with non-Hodgkin lymphoma reported injection site pain, malaise and myalgia reported after RIV.	Safety profile of recombinant haemagglutinin vaccine was comparable to traditional IIV, except for a higher incidence of chills.
Chinese adults aged <65 years	[73]	Post-licensure study adults aged 18-64 years who identify as Chinese ethnicity within KPNC. 15,574 received RIV and 27,110 received QIV	• Demographics were similar between groups. 15.5% of subjects had a comorbidity of interest within the last 2 years (diabetes, asthma most common). Similar proportion of each group were pregnant. No statistical difference in AESI within 41-day risk window. Mild outcomes may not have been captured if no medical care sought • Day 0-2: 1 case of acute hypersensitivity and one fever in QIV group. • Days 0-13: fever (5), • Day 0-41 convulsion (1 RIV 2 QIV); pericarditis (1 QIV) non-infectious pleural effusion (1 each); ITP (4 RIV 14 QIV). Deaths 8 RIV, 27 QIV (p = 0.07)	No safety concerns were identified regarding RIV in Chinese adults.

Outcomes/ group	Ref	Study type / Participants	Results	Findings
Pregnancy	[74]	Post-licensure KPNC observational study subset of 48,781 (14,981 RIV4 and 33,800 QIV) pregnant people and 47,394 live births during 2018/19 and 2019/20 seasons.	The proportions of adverse pregnancy outcomes and neonatal outcomes were similar between vaccines (RIV vs QIV): • spontaneous abortion aOR 0.95 (0.85-1.05) • preterm labour 1.06 (0.99-1.14); preterm infant 0.98 (0.91-1.05) • stillbirth / fetal death 0.84 (0.68-1.04) • congenital/fetal abnormalities in pregnancy 1.00 (0.96-1.06); at birth 1.01 (0.97-1.05) • pre-eclampsia 1.01 (0.96-1.06) • placental abruption 1.12 (0.96-1.31)	No statistical difference was found for any pregnancy outcome, birth or neonatal/infant outcome between those who received RIV4 or QIV during pregnancy. Data support recommendation for influenza vaccination in pregnancy with recombinant or inactivated influenza vaccines.
Immunogenicity				
Comparison with standard IIV	[75]	RCT adults aged 18-49 years, 998 received RIV4 and 332 standard QIV. (note strains used for HAI assay were egg-grown)	• RIV4 met coprimary endpoints and non-inferiority with QIV (seroconversion rates and HAI GMTR at 28 days) for A/H1 (California), A/H3 (Texas) and B/Yamagata (Massachusetts) antigens but not B/Vic (very low GMTs for both vaccine groups). • Antibody response to A/H3 strain were significantly higher for RIV4 vs QIV.	RIV had an acceptable immunogenicity profile in adults aged 18-49 years. It induced significantly higher antibody response against A/H3 strains than QIV.
Frequently vaccinated HCW	[76]	RCT (SHIRI) in 415 HCW in 2 Israeli hospitals during 2019/20 season vaccinated with RIV4 or QIV	• RIV4 vs QIV HAI GMTR: o A/H1N1: 2.0 (1.7-2.7) o A/H3N2: 1.6 (1.3-1.9) egg-based virus; 2.3 (2.0-2.8) cell-based virus o B/Victoria: 1.1 (0.9-1.4) o B/Yamagata: 1.8 (1.4-2.2) • RIV4 induced higher HAI titres against vaccine reference viruses (except B/Vic) among frequently and infrequently vaccinated HCW (lower bound GMTR 95% CI ≥1.0) • Seroconversion rate difference RIV vs QIV: o A/H1N1: 29.0% (20.1-27.8) o AH3N2: 22.4 (13.1-31.8) egg; 36.9 (28.3-45.6) cell o B/Vic: 8.9 (2.3-15.5) o B/Yam: 22.3 (14.4-30.8)	RIV4 had improved immunogenicity against influenza vaccine virus strains over QIV among health care workers who were frequently and infrequently vaccinated against influenza.
	[77]	RCT, open-label HCW aged 18-64 years from 2 integrated healthcare systems in the US (Texas and Oregon). Season 1 (2018/19) randomised to QIV, QIVc or RIV4. Season 2 QIVc or RIV4 groups re-randomised to QIVc or RIV4. (n= 101 QIVc/QIVc, 106 QIVc/RIV4, 73 RIV4/QIVc, 74 RIV4/RIV4) and 60 QIV/QIV reference group).	• Compared with QIV/QIV group • all groups had higher the mean fold rise in HAI GMT. • GMTR ($p<0.07$) ranged from 1.8 (1.2-2.9) B/Yam to 2.0 (1.2-3.4) A/H1N1 in year 2. • Repeat vaccination with non-egg-based vaccine induced higher antibody titres to cell-based virus strains.	Recombinant influenza vaccine elicited higher antibody titres than QIVc or QIVe. It is unclear whether this is due to the higher antigen dose or differences in the immune response to the recombinant HA antigen. RIV, received in preceding season or current season, induced robust antibody responses against all vaccine components except A/H3N2 (for RIV/QIVc group).

Outcomes/ group	Ref	Study type / Participants	Results	Findings
CD4 T cell response	[78]	Adults (18-49 years) given TIV, TIVc or RIV over 3 seasons (2015-2018). T cell response to HA assessed by EliSpot or intracellular staining assays. Antibody response measured HAI and ELISA. Blood collected days 0, 7, 14, 28 and 180 post vaccination	CD4 T cells (cytokine response to HA d0 to d14) • RIV induced greater response for all HA types, significantly higher than TIVc and TIV for H1 (P=0.014 and p=0.006) and H3 (p= 0.002 and p<0.0001) consistent with higher immunogenicity. • There was individual variability in response to HA types. • When compared with hd-TIV (with higher Ag content than RIV), RIV elicited a higher CD4 T cell expansion but not statistically different in this age group.	RIV induced robust and statistically significant CD4 T cell responses, compared with TIV or TIVc. Although higher antigen content could be a factor, RIV performed better than hd-TIV.
Comparison A/H3N2 response	[79]	85 healthy adults (median aged 23 years, range 18-49 years). Compared responses to TIVe (Fluzone), hd-TIV (Fluzone high-dose), RIV3 (Flublok), TIVc (Flucelvax) during 2017-18 season. Neutralisation assay (FRNT) using egg-adapted H3N2, cell-based H3N2 and 2 wild-type H3N2 and H1N1. ELISA against recombinant wild-type 3c2.HA. (NCT03068949)	• N=23 for TIV3, TIVc, RIV3 and 16 for hd-TIV 28 days post vaccination, FRNT titres to wild-type 3c2.A and 3c2.A2 • 3.9 to 4.3 folder higher RIV vs TIV (P<0.001) • TIVc = TIVe, significantly lower than RIV (p<0.001 and p=0.003) Anti-H3 ELISA titres closely mirrored FRNT titres. • 2.1 – 3.0-fold higher RIV vs TIVc or TIVe (p=0.076 and =p=0.002) Findings were reflective of relatively low effectiveness of TIVc and TIVe in 2017/18 season Compared hd-TIV (4 times TIV HA) and RIV (3 times TIV HA) • Hd-TIV vs TIVe = 3.2-fold higher FRNT titre • Titres similar with hd-TIV and RIV, higher proportion of RIV group seroconverted to wild-type H3N2 virus ○ 3c2.A 52% (12) RIV vs 38% (6) hd-TIV ○ 3c2.A2 61% (14) vs 38% (6)	Antigen match and vaccine dose are both important to elicit optimal antibody response to contemporary wild-type A/H3N2 viruses.
Antibody response	[80]	Plasmablasts isolated from healthy adults aged 18-49 years vaccinated with RIV (n=6) or TIVc (n=5). Comparing 42 Flublok (RIV) and 38 Flucelvax (TIVc) induced monoclonal antibodies avidity, cross-reactivity and selectively towards HA domains	• Vaccine induced by RIV had greater proportion of mAbs targeting epitopes near receptor-binding domain (head) of HA than QIVc. • Both induced similar frequency of stalk-reactive mAbs and stalk-reactive antibody secreting cells. • In vaccinated mice, naïve to influenza, vaccines induced similar frequencies of stalk-reactive Ab, showing HA-head immunodominance was independent of immune memory (ie immune imprinting was not a major bias in the human cohort)	Both vaccines have similar immunogenicity, but RIV has preference towards RBD on HA head.

Older adults Comparative immunogenicity enhanced IIV (more details given in Table 9)	46	RCT, community-dwelling adults aged 65-82 years in Hong Kong (Oct 2017-Jan 2018). Comparing QIV, aTIV, hd-TIV, RIV4.	• In the assays, A/H1N1 and A/H3N2 strains were egg-propagated for HAI and micro-neutralisation (MN) assay used cell-propagated A/H3N2. • At 30 days post vaccination, mean fold rise in HAI titres and MN were significantly higher in all groups over standard vaccine. • MFR in MN assay: Recombinant (4.7-fold) vs standard QIV (2.3-fold). • Proportion with >4-fold rise to HAI titres ≥1:40 were statistically higher for all 3 enhanced vaccines: o A/H1N1 RIV4 60% (53-67%) vs 42% (36-50) for QIV o A/H3N2 RIV4 56% (48-63%) vs 41% (34-48%) for QIV o B Victoria: RIV4 44% (34-51%) vs 48% (41-56%) for QIV • Boosting of IFN-γ CD8+ T cell responses also observed with enhanced vaccines, particularly to B/Victoria in which there was no significant rises for standard QIV • Antibody responses to cell-propagated a/H3N2 using MN were significantly higher for the RIV4 than the other vaccines.	This study found that all of the enhanced influenza vaccines had improved immunogenicity compared with standard QIV for A/H3N2 and A/H1N1 influenza in older adults. Recombinant QIV induced particularly high antibody response to the cell-like H3N2 strain. This study could not extrapolate immunogenicity to effectiveness.
Effectiveness and efficacy				
Adults aged ≥18	72	SR found 2 studies on efficacy published up to February 2020	Since this study only evaluated two efficacy studies, these individual studies are given below.	
	81	Placebo controlled RCT 4,648 adults aged 18-55 (mean age 32.5 years) across 24 centres in the US during 2007/08 season. Randomised 1:1 RIV or placebo. Completed weekly diary to identify those with influenza symptoms, returned to clinic if had any ARI and swabbed.	• Efficacy endpoint – culture confirmed CDC-ILI case definition (fever ≥100°F [38°C]) plus sore throat or cough) • 178/582 tested had influenza virus, 120 influenza A (68% with CDC-ILI) and 59 influenza B (69% with CDC-ILI). o Only 8 were antigenically identical to vaccine strain. Vaccine mismatched H3N2 predominant circulating virus and high prevalence of B/Yamagata (not included in vaccine) o Unable to obtain efficacy estimate against vaccine strain-specific disease. o Overall efficacy of RIV against culture-positive CDC-ILI was 44.6% (18.8-62.6%), regardless of strain. o Significant mismatch for influenza B (VE influenza A 54.4% (26.1-72.5) and influenza B 23.1%; -49.0-60.9%).	Study provided evidence of protective effect from a recombinant HA vaccine. It supported protection in a primed population with a pure HA vaccine. Minor differences in HA glycosylation (between insect and mammalian cells) and use of a synthetic uncleaved HA precursor did not prevent an effective immune response in adults.

Efficacy, aged ≥50 years	[82]	RCT in US compared RIV4 with QIV. 8604 adults aged >50 years randomised to either vaccine (95% per-protocol population) PCR confirmed Protocol defined ILI (≥1 each respiratory and systemic illness, regardless of severity) >14day post vaccination.(Protein Sciences, NCT02285998)	• PCR confirmed influenza attack rate: ○ RIV 2.2% (96 cases / 4303 participants); TIV 3.2% (138 / 4031). ○ 181 cases A/H3N2, 47 cases influenza B and 6 non-typeable influenza A. ○ Probability of ILI was 30% lower with RIV4 than QIV (95% CI 10-47, p0.006). ○ Cumulative incidence PCR confirmed ILI rVE RIV4 vs QIV HR 0.69 (0.53-0.90, p=0.006) ○ Post-hoc analysis, rVE RIV4 against influenza A HR 0.63 (0.48-0.86, p=0.003). No difference relative to influenza B.	Recombinant influenza vaccine provided 30% better protection than standard-dose QIV against PCR-confirmed influenza like illness in adults aged 50 years and over.
Effectiveness, adults aged 50 to <65 years	[83]	Cluster randomised observational study KPNC high dose RIV4 or standard dose QIV during 2018/19 and 2019/20 seasons. Included 1,630,328 adults aged 18 -64 years (632,962 RIV group vs 997,366 TIV) (Sanofi, NCT03694392) Total 1386 PCR confirmed influenza.	• Aged 50-64 y 559 cases RIV4 and 925 cases QIV (PCR+ influenza) ○ relative effectiveness 15.3% (5.9-23.8, p=0.002) ○ Influenza A rVE 15.7% (6.0-24.5, p=0.002) ○ RIV was improved protection for individuals with underlying conditions (CVD, Hospitalised influenza rVE ○ PCR-confirmed influenza 15.9 (-9.2-35.2, p=0.19) ○ Community acquired pneumonia 16.7 (-5.6 to 34.4, p=0.13) ○ Cardiorespiratory event 2.4 (-8.1 to 11.9, p=0.64)	RIV was around 15% more effective than standard IIV against PCR confirmed influenza in adults aged 50-64 years. No significant difference was seen against more severe hospital outcomes.

Abbreviations: AE – adverse events; AEFI – adverse events following immunisation; 95% CI – 95% confidence interval; ELISA – enzyme linked immunosorbent assay; FRNT – focal reduction neutralisation tests; GMTR – geometric mean titre ratio; HA – haemagglutinin; HAI – haemagglutinin inhibition assay; HD – high dose; IPTW - inverse probability of treatment weighting; ILI – influenza-like illness; IRME – influenza-related medical encounter; IRR – incidence rate ratio; KPNC – Kaise Permanente Northern California; m – months; mAb – monoclonal antibody; MFR – mean fold rise; QIV – quadrivalent inactivated influenza vaccine; RCT – randomised controlled trial; RIV – recombinant influenza vaccine; rVE – relative vaccine efficacy/effectiveness; SAE – serious adverse events; SD – standard dose; SR – systematic review; TIV – trivalent influenza vaccine; US – United States [of America]; VE – vaccine efficacy/effectiveness; vs – versus; y - years

Table 12: Live attenuated influenza vaccine

Outcomes	Ref	Study type / Participants	Results	Findings
Safety				
Children and adults with asthma and/or recurrent wheeze	[85]	SR (AstraZeneca) LAIV-AA aged 2-49 years with asthma diagnosis (any severity) or recurrent wheeze. 12 studies in children and 2 studies in adults with 1.2 million participants; included studies from 1997-2017, over 20 influenza seasons	• Study controls – 9 use IIV, 2 unvaccinated, 2 self-controlled over ref time periods, 1 placebo, 1 study had no-asthma cohort and 1 baseline asthma symptoms • No studies found increased risk of significant clinical outcomes post vaccination in participants with a history of asthma/wheeze. – no differences in asthma exacerbations, wheezing or healthcare utilisation. • No data for adults aged ≥50	LAIV (AA) was well tolerated with no safety concerns in individuals aged 2-49 years with asthma or history of recurrent wheeze.
	[86]	SR (AstraZeneca) LAIV vs IIV, 15 studies GRADE assessed ages 2 to 49 years with asthma/recurrent wheeze. Study heterogeneity prevented meta-analysis.	• No differences in patient-reported outcomes in 87% of studies between LAIV and IIV (all ages, very low to moderate certainty of evidence) • Reportedly higher incidence of rhinitis and lower incidence of hospital visits (inpatient/ED) and wheezing after LAIV vs IIV.	Comparable safety outcomes between LAIV and IIV in people with asthma or recurrent wheeze, irrespective of disease severity.
Children with asthma	[87]	142 children aged 5-17 years randomised QIV or LAIV4. (Nashville, US) Monitored for asthma symptoms for 42 days post vaccination.	• Vaccine reactogenicity was similar between groups. • Sore throat and myalgia were more common in LAIV group • 8/74 (11%) LAIV and 10/68 (15%) QIV experienced asthma exacerbation within 42 days. LAIV remained non-inferior to QIV when adjusted for asthma severity (p=0.71) • No significant differences in frequency of asthma symptoms, change in PEFR or asthma control test scores in 14 days post vaccination.	LAIV was not associated with an increase in asthma-related symptoms or frequency of asthma exacerbations in children aged 5-17 years with asthma. Data support re-examining precautions around the use of LAIV in children with asthma.
	[88]	Prospective phase IV interventions study, 14 specialist clinics in UK. LAIV administered under medical supervision, follow-up of asthma symptoms for 72h and 4 weeks, using questionnaires.	• 478 children (median age 9.3 years, range 2-18 years) with diagnosed asthma or recurrent wheeze, 44% on high-dose corticosteroids and 31% with severe asthma. • No significant difference in asthma symptoms with 4 weeks (median change 0, p=0.026). 47 children (14.7% , 95% CI 11-19%) reported severe asthma exacerbation within 4 weeks requiring systemic corticosteroids. 4 cases within 72 hours of vaccination. • Rate of acute AE 3/478 (0.63%, 95% CI 0.13-1.82) – inline with reported rate in normal population • 139 reported delayed AE (2-72 hours) likely associated with vaccine, 28/440 (6.4%) reported wheeze within 72 hours. More delayed AE in younger ages (reflective of viral infections in this age group). No association with baseline asthma control. • After 72 hours – no association between baseline asthma control and odds of exacerbation in those age 2-4 and 5-11 years (p=0.69 and 0.65)	LAIV appeared to be well tolerated in most children with asthma or recurrent wheeze, including those with severe or poorly controlled asthma. No evidence that LAIV administration resulted in an adverse event signal in young people with severe or 'difficult' asthma, including in preschool children with severe wheeze. Supports UK guidance that 'children with asthma on inhaled corticosteroids (irrespective of dose) can be safely given LAIV'. Although it is not recommended in those with an acute exacerbation of asthma symptoms within the previous 72 hours.

Outcomes	Ref	Study type / Participants	Results	Findings
Children with HIV infection	89	NACI SR and recommendations on use of LAIV in children with HIV infection	• Insufficient data to detect uncommon AE • 3 studies reported AEFI with LAIV in 191 children and young adults with HIV. • Comparable rates of AEFI with and without HIV • Vs IIV – LAIV associated with increase in nasal congestion and runny nose. • No serious AEFI attributed to LAIV • No reports of AEFI to CAEFISS in HIV-infected individuals vaccinated with LAIV. • Vaccine virus shedding did not differ by HIV status.	LAIV may be considered for children aged 2-17 years who are 1) receiving highly active antiretroviral therapy (HAART) for ≥4 months; 2) CD4 count ≥500/µl ages 2-5 years or ≥200/µl ages 6-17 years; 3) HIV plasma RNA <10,000 copies/mL. Remains contraindicated for adults due to insufficient data.
In adults	103	SR to Feb 2021 PubMed/Scopus, 16/22 studies examined safety, 12 used self-reported AE. Heterogeneous studies, only in adults.	• In adults - only rhinorrhoea, nasal congestion and sore throat were significantly associated with LAIV compared with placebo. With very low invasiveness. • No SAE significantly associated with LAIV compared with placebo	
Chinese children	92 105	Phase 3 RCT, 2016/2017 season. children aged 3-17 years (1500 participants per group), placebo controlled incl for safety analysis (Chinese LAIV GANWU vaccine)	• No significant differences in solicited or unsolicited AE. • Nasal congestion (16.5% vs 13.7%), headache (6.8% vs 5.1%) and muscle pain (1.4% vs 0.7%) were more frequent in LAIV recipients.	LAIV is safe among Chinese children aged 3 to 17 years.
Immunogenicity				
Mucosal and systemic response	90	RCT, 40 healthy adults (median age 22, range 19-29). Nasal samples taken 24h, 72h and 168h and day 28 post vaccination.	• Antiviral immune response seen in nasal mucosa within days of inoculation. • Broad titre increases in mucosal and serum antibody responses, strongly compartmentalised. • Activation of circulating follicular T and B cells were associated with serum IgG. But not with mucosal IgA, which was associated with activation of peripheral CD8+ T cells. • Participants who did not mount a blood antibody response did have raised virus-specific mucosal IgA.	Reliance on peripheral blood antibody responses may miss relevant mucosal antibody responses against respiratory viruses. Efficacy of LAIV may result from antibody responses within the nasal mucosa that are not reflected in serum antibody levels. Mucosal and blood antibody responses to LAIV were distinct and compartmentalised.

Outcomes	Ref	Study type / Participants	Results	Findings
Cell-based vs LAIV in children	21	RCT, participants aged 4-21 years in US; 112 received QIVc and 118 LAIV. MIADA and HAI pre and 28 days post vaccination. (as described in Table 8)	• HAI and immunoglobulin isotype response to QIVc > LAIV, significant increases in IgG but not IgM or IgA. • Some level of HAI and IgG response expected but with a minimal HAI response. • Youngest (4-11 year olds) had highest HAI response to LAIV, except for A/H3N2. • There were significant age-related differences responses following LAIV across childhood. Prior LAIV associated with higher current season QIVc response. • Immunoglobulin assays correlated strongly with and confirmed HAI titres and MFI values for both vaccines. • Immunoglobulin assays can detail a range of responses to different regions of HA epitopes (head, stalk, and cross-reactivity) and nucleoprotein antigens.	Age and prior season vaccination play a role in the immune response in children and young adults to both QIVc and LAIV. LAIV can prime a more robust response to IIV in the second season. HAI titres can provide meaningful representation of day 28 response to vaccination, but do not represent the full immune response. And do not predict vaccine effectiveness. QIVc induced higher HAI and MFI than LAIV, but varied by age and type of vaccine given previously.

Antibody titres as correlate for efficacy	91	Data from RCT (FLUVACS) in 2007/08, comparing IIV and LAIV adults aged 18-49 years in US.	• For LAIV:
			  ○ No evidence that VE was associated with post vaccination or fold-rise in HAI or NAI titres following LAIV (p>0.4).
			  ○ VE did not depend on previous vaccination or baseline HAI or NAI titres
			• For IIV:
			  ○ VE increased (p=020) with day 30 HAI titre but more significantly with NAI (p=0.04)
			  ○ No evidence of fold-change in post vaccination HAI or NAI was associated with VE.
			  ○ VE increased with NAI titre in those previously vaccinated but decrease with increasing NAI in those previously unvaccinated.
			• Difference potentially influenced by high/more durable baseline NAI protection in previously unvaccinated controls who may have previous immunity through natural infection. LAIV may protect in a similar way.
				No evidence that LAIV VE depended on previous vaccination or baseline HAI or NAI titres. In contrast, previous vaccination and baseline NAI titres significantly modified IIV VE.
				IIV vaccination in those with high antibody levels from natural immunity may not confer protection greater than that provided by previous immunity.

Chinese children	92	Phase 3 RCT, 2016/2017 season. children aged 3-17 years (1500 participants per group) placebo controlled incl substudy 499 per group for immunogenicity (Chinese LAIV GANWU vaccine)	• Comparable baseline HAI GMTs between groups at baseline
			• After vaccination GMTs for all viral types were higher than placebo.
			• Greatest geometric mean fold increases (gMFI) were seen against H3N2 and B in those aged 3 – 5 than ages 5 – 12 years and 12 – 17 years
			  ○ H3N2: 2.73 (2.10 - 3.55) vs 1.58 (1.46 – 1.70; p< 0.001) and 1.63 (1.45 – 1.83; p = 0.04)
			  ○ B: 3.63 (2.85-4.62) vs 2.17 (1.99 – 2.37) and 1.78 (1.58 – 2.00)
			• Seroconversion – significantly higher for vaccine group than placebo (any type 43.8% vs 13.5%, p<0.001). Variability in significance when stratified by age vs influenza type, lowest for ages 12-17 against influenza A.
			• Seroconversions and gMFIs were not considerable – higher baseline immunity against influenza A in older age groups may have reduced observable impact.
				LAIV is immunogenic in children aged 3-17 years in China.
				HAI titres may not be as good a measure of LAIV immunogenicity as for IIV – serum responses tend to be lower and cellular and mucosal responses may be more important.

Outcomes	Ref	Study type / Participants	Results	Findings
Preexisting influenza immunity	93	UK phase 4 open-label study, 362 children aged 6-14 years during 2017/18 season (FluShed study). • Nasal samples for IgA (prior) and crevicular fluid (oral) collected (d0 and day 21-28) via swabs. • Nasal swabs for viral shedding day 1, 3, 6 post vaccination (detected by RT-PCR). • Influenza-specific IgA and IgG ELISA	• No differences at baseline, IgA significantly higher for H3N2 >H1N1 or B/Bris and B/Phu > H1N1 or B/Bris • Adaptive response – increase in H1N1 IgG in oral fluid but not for H3N2 IgG. No correlation in baseline IgA and fold-change in IgG (H1 or H3). • No significant difference in baseline IgA and children who had detectable vaccine virus shedding vs non-shedders • Underlying URTI (asymptomatic infection) did not alter vaccine immunogenicity (83 children)	Neither the presence of influenza-specific IgA nor concurrent viral URTI impact on the immunogenicity of LAIV. No relationship was observed between baseline nasal influenza-specific IgA and fold-changed in H1N1 or H3N2=specific IgG. The findings support the use of LAIV in annual influenza programmes and in the presence of concurrent URTI.
Effectiveness				
Comparative effectiveness LAIV4 and QIV in children	97	SR / MA (AstraZeneca)– ten studies across 2019/20 to 2022/23 seasons in the EU (ages 2-17) and US (aged 6m to 17, low coverage) During COVID-19 pandemic, influenza programmes were expanded to include children.	• VE against influenza infection: o for all strains: LAIV4 61.9% (95% CI 53.0 – 69.1) vs QIV 45.7% (33.2 – 55.8) o Individual strains VE for 2022/23 season – 75% (53.0 – 87.7) vs 58.5% (38.2 – 72.1)	VE of LAIV4 and QIV was moderate in children and generally comparable between vaccine formulations and seasons. These results demonstrated that influenza vaccination programmes in children are effective.
Real-world effectiveness in children ≤19 years	98	SR / MA (AstraZeneca). Compared with IIV. 109 studies over three time periods: 2003/4 – 2008/9 (prior to A/H1N1pmd09 pandemic) n=8 2010/11 – 2016/17 (following H1N1 pandemic) n=76 2017/18 – 2022/23 (after update of LAIV strain production process) n=34	Effectiveness varied across seasons – aVE point estimates ranged 30-66% LAIV and 28-72% IIV (wide Cis). Likely reflects vaccine-match to circulating virus strains. Pooled estimates aVE: • LAIV: o 2010-17 49% (95% CI 39 - 57) o 2017-23 51% (95% CI 39 - 60) • IIV: o 2003/4 52% (95% CI 38 - 62) o 2010-17 44% (95% CI 39 - 49) o 2017-2023 48% (95% CI 36-57) • Comparable effectiveness generally, except IIV >LAIV during 2010-2017 and LAIV >IIV during 2017-2023. • Greater effectiveness against influenza B during 2017/18 to 2022/23 – aVE 81% (66-90) vs 49% (31-63), predominantly during 2017/18 and 2019/20.	While some fluctuations occurred, LAIV and IIV were shown to have comparable effectiveness, of around 50%, in children against all influenza. LAIV appears to be more effective than IIV against influenza B in children.

Outcomes	Ref	Study type / Participants	Results	Findings
Effectiveness against severe disease in ages 2 – 6 years	100	Screening method, vaccine coverage in 227 children hospitalised with lab-confirmed influenza compared with children in general population. During first 3 seasons of LAIV programme (2013/14, 2014/15, 2015/16 season UK). Cases were identified through USISS surveillance system. Vaccine history for a case was obtained via a standard data collection proforma from the case's general practitioner.	Of 277 cases: • 69.6% (n=157) in 2015/16, 21.6% (49) 2014/15 and 8.8% (20) 2013/14 season. • 50.7% A/H1N1pdm-09; 15.4% A/H3N2; 23.8% B and 10% influenza A no subtype. • 55 (24.2%) vaccinated cases, 53 with LAIV Adjusted VE against influenza hospitalisation (by local authority, age and week/month of infection): Overall – 50.1% (31.2 – 63.8) • 2013/14 ages 2-3 years 50.5% (-39.0 - 82.3) • 2014/15 preschool (ages 2-4 years) 43.3% (-12.1 to 71.3) • 2015/16 preschool 49.4% (22.8-66.9); school (ages 5-6 years) 62.6% (2.6-85.6) aVE Children aged 2-4 y with risk group status (69.9% unvaccinated and 57.1% vaccinated cases had missing information on risk group status), • all cases (not adjusted for risk) 48.1% (27.2-63.1) • cases with known risk 44.2% (3.3-67.8) • unknown risk, assumed to have risk factor 69.9% (57.6-78.6) • unknown risk, assumed no risk factor 57.6% (34.1-72.7)	Overall effectiveness of LAIV against hospitalisation in children over three seasons was 50%. Vaccine uptake of hospitalised cases was 24%.

Hospitalisation and mortality in ages 2 – 6 years	101	Cohort study using linked data from Danish nationwide health-care registries, 95,434 children aged 2-6 years vaccinated Oct 2021 – Jan 2022 (H3N2 predominant season, with low previous influenza experience in young due to COVID-19 pandemic) matched to 95,434 unvaccinated controls.
		Follow-up to May 2022 (peak in influenza cases in late March)
		In Oct 2021, expanded LAIV vaccine eligibility to all children aged 2-6 years. Two doses LAIV recommended.
			• 784 children had influenza-related hospital contact.
			• LAIV4 vs no vaccine against influenza-related hospital contacts ≥14 days after vaccination (76 vs 210 events):
			  ○ IRR 0.36 (95% CI 0.27-0.43)
			  ○ Est VE 64.3% (53.6-72.6)
			  ○ No statistically significant effect after one dose VE 28.9% (-16.4 to 56.6) vs 74.3% (64.2 to 81.5) after two doses.
			• Against influenza-related hospital admission >12h (24 vs 38 events)
			  ○ IRR 0.63 (0.38-1.05)
			  ○ Est VE 36.9% (-5.2 to 62.1.)
			  ○ Cohort and test-negative design sensitivity analyses – VE 38.1% (3.7-60.2%) and 46.4% (10.6-68.0%), statistically significant
			• LAIV not associated with reduction in:
			  ○ Respiratory tract infections IRR 1.14 (0.94-1.38)
			  ○ Wheezing or asthma 1.04 (0.83-1.31)
			  ○ Antibiotic prescription for any respiratory infection 0.97 (0.93-1.00)
			VE similar in children with or without coexisting influenza risk factors
			
			When influenza-related outcomes were disregarded for the first 30 days (due to risk of false positive influenza test from LAIV vaccination), VE increased:
			• Hospital contact – 69.7% (59.9-77.2%)
			• Hospital admission – 52.7% (17.1-73.0%)
				LAIV was moderately effective in preventing A/H3N2-dominant influenza-related hospitalisation (64% hospital contact and 37% hospital admission) of young children but was less able to prevent hospitalised secondary outcomes of influenza infection. The study was not designed to determine differences in severity for these outcomes, beyond need for hospitalisation and did not differentiate influenza from other respiratory pathogens for these outcomes.
				False-positive influenza virus testing in first few weeks after vaccination underestimated vaccine effectiveness.

Outcomes	Ref	Study type / Participants	Results	Findings
Impact on Group A Streptococcus (GAS) infection	[102]	Cumulative incidence of GAS, scarlet fever and invasive GAS (iGAS) were compared in LAIV pilot and non-pilot areas in the England prior to LAIV introduction (2010-2013) and post programme seasons (2013-2017) in two age groups (ages 2-4 years and 5-10 years).	• Preprogramme seasons, incidence of all GAS infections was higher in pilot areas than non-pilot (IRR >1) • Post-programme season – GAS, scarlet fever and iGAS were lower in pilot areas in targeted groups. • Comparison cumulative incidence pre- and post-programme in GAS: ○ Age 2-4 years: 1.26-fold increase in pilot areas was lower than 2.03 increase in non-pilot (rIRR 0.62; 95% CI 0.43-0.9; p=0.011) ○ Age 5-10 years: 1.19-fold increase < 2.10-fold increase (rIRR 0.57, 0.45-0.71; p <0.001) ○ iGAS – aged 2-4, rIRR 0.58 (0.21-1.65, p=0.31); no difference for 5–10-year-olds rIRR 1.1 (0.34-3.60) ○ scarlet fever in both age groups – no difference. • Difference in non-target age groups were varied and minimal pre and post pilot.	Findings suggest that reductions in influenza by vaccinating children with LAIV contribute to reduction in secondary bacterial infections. Most apparent in 5–10-year age group with the highest burden of GAS infections.
Efficacy in adults	[103]	SR, 22 studies to Feb 2021 Limitation of small numbers in studies.	• Review did not find any RCTs in high-risk participants (breastfeeding, immunocompromised, elderly, healthcare workers) • None of the studies considered adults over 65 years or infants under 2 years.	Results support LAIV efficacy compared with placebo but meta-analysis showed lower efficacy than IIV. Further reviews on efficacy and vaccine acceptance required.

Abbreviations: AE – adverse events; AEFI – adverse events following immunisation; aVE – adjusted vaccine effectiveness; 95% CI – 95% confidence interval; EMR – electronic medical records; GB – Great Britain; GI – gastrointestinal; gMFI – geometric mean fold increases; HA – haemagglutinin; HAI – haemagglutinin inhibition assay; hd-TIV – high-dose trivalent influenza vaccine; IFN – interferon; IPTW - inverse probability of treatment weighting; iGAS – invasive group A streptococcal disease; IRME – influenza-related medical encounter; IRR – incidence rate ratio; KPSC – Kaise Permanente Southern California; LAIV – live attenuated influenza vaccine; m – months; MFI – median fluorescent intensity; MFR – mean fold rise; MIADA – multiplex influenza antibody detection assay; QIV – quadrivalent influenza vaccine; RCT – randomised controlled trial; rIRR – relative incidence rate ratio; rVE – relative vaccine efficacy/effectiveness; SAE – serious adverse events; SR – systematic review; TIV – trivalent influenza vaccine; US – United States [of America]; VE – vaccine efficacy/effectiveness; vs – versus; y - years

Search strategies

OVID Medline

Search strategy	results
Keywords Influenza Vaccines / and Adjuvants, Immunologic /	1898
limit to English language, humans and year 2019 to current (24 March 2025)	425
Abstract review – selected	73
Live attenuated influenza vaccine.m_titl.	320
limit to English language, humans and year 2019 to current (24 March 2025)	96
selected	63
high doses influenza vaccine.m_titl.	37
limit to English language, humans and year 2019 to current (24 March 2025)	12
*Influenza Vaccines/ and cell-based influenza vaccine.mp.	19
selected	9

PubMed

comparison "influenza vaccines" in adults 2020-2025 -results 110 selected 23

comparison influenza vaccines 2020-2025 results 435 selected

'Cell-based influenza vaccine' NOT COVID-19, 2019-2025, English – 189 results, selected 45

'Comparison of cell-based and egg-base influenza vaccines' 2019-2025 9 results, selected 6

Recombinant influenza vaccine – 3115; narrowed to "recombinant influenza vaccine" = 95; 2019-2025 = 55, selected 24

FluBlok vaccine 20219-2025 – 33 results, 9 selected – all removed as duplicates

Final Endnote library contained 296 journal articles, webpages, press-releases, government and associated reports, and product information monographs/data sheets.

AstraZeneca and CSL Seqirus provided additional literature and unpublished data from conference proceedings.

Further literature was obtained during the review from PubMed and from publicly available grey literature.

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