Recent advances in the influenza virus vaccine landscape: a comprehensive overview of technologies and trials

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SUMMARY

In the United Kingdom (UK) in 2022/23, influenza virus infections returned to the levels recorded before the COVID-19 pandemic, exerting a substantial burden on an already stretched NHS through increased primary and emergency care visits and subsequent hospitalisations. Population groups ≤4 years and ≥65 years of age, and those with underlying health conditions, are at greatest risk of influenza-related hospitalisation. Recent advances in influenza virus vaccine technologies may help to mitigate this burden. This review aims to summarise advances in the influenza virus vaccine landscape by describing the different technologies that are currently in use in the UK and more widely. The review also describes vaccine technologies that are under development, including mRNA, and universal influenza virus vaccines which aim to provide broader or increased protection. This is an exciting and important era for influenza virus vaccinations, and advances are critical to protect against a disease that still exerts a substantial burden across all populations and disproportionately impacts the most vulnerable, despite it being over 80 years since the first influenza virus vaccines were deployed.

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INTRODUCTION

Whilst the influenza virus has been in circulation for centuries, and vaccines available for over 80 years, the last two decades have seen substantial advances in influenza research and control, including the introduction of several new technologies for vaccination. In this review we first provide a brief overview of the current epidemiological and vaccine policy landscape, before describing the available vaccine technologies and the related clinical data regarding their efficacy and effectiveness.

Influenza burden

Influenza viruses cause a substantial disease burden within the United Kingdom (UK) and around the world (1-5). In 2017, there were an estimated 145,000 deaths and 9.5 million hospitalisations globally caused by influenza-related lower respiratory tract infections (6). Following a reduction in the number of influenza cases during the COVID-19 pandemic, recent data suggest that the number of cases are now comparable with levels recorded before the pandemic (Fig. 1) (7, 8). In England during the 2022/23 influenza season, there were 8,751 hospitalised cases of confirmed influenza virus infection and an estimated 14,623 excess deaths associated with influenza (9). This is compared with 5,144 and 8,800 excess deaths in the 2018/19 and 2019/20 seasons, respectively (9).

Children ≤4 years and adults ≥65 years of age have the highest risk of influenza-related hospitalisation (10). Other population subgroups at risk of severe influenza disease or complications include those with chronic medical or immunosuppressive conditions, including transplant recipients, and healthcare workers who are at high risk of increased exposure to influenza virus (1, 11-14). The medical conditions considered at risk and for whom influenza virus vaccination is recommended in the UK are presented in Table 1; these groups will vary somewhat between countries (11, 15). In addition, influenza virus infection increases the risk of hospitalisation in pregnant women and can cause harm to the developing foetus (16, 17). Inactivated influenza virus vaccination is therefore recommended

to pregnant women during any trimester, providing protection both to the mother and, passively, to the infant in the first 2–3 months (18, 19). Evidence supporting this recommendation includes results of a test-negative case control study demonstrating that maternal influenza virus vaccination was associated with a vaccine effectiveness of 53% (95% confidence interval [CI]: 30, 68) against influenza-related hospitalisation and emergency department visits in infants less than 3 months of age (13).

The acute respiratory symptoms associated with influenza virus infection are widely reported; however, more recent studies have highlighted that influenza virus infection is associated with a broad range of adverse outcomes and long-term effects, including exacerbation of underlying medical conditions (20, 21), increased susceptibility to secondary bacterial infections (22), cardiovascular events such as myocardial infarction (23-25), functional decline in older individuals with high baseline frailty (26), and complications in pregnancy (27). Therefore, reducing disease severity through seasonal influenza virus vaccination may lead to a range of health benefits (28-32).

Influenza virus characteristics

There are four types of influenza virus; of these, influenza A and B viruses cause seasonal epidemics (33). Influenza A viruses are classified into subtypes, whereas influenza B viruses are classified into two different lineages, B-Victoria and B-Yamagata (33). Influenza A viruses exist as different subtypes with varied antigenic characteristics according to the type of haemagglutinin (HA) and neuraminidase (NA) glycoproteins on the virus surface; these glycoproteins facilitate infection of host cells (34-36). HA enables entry into the host cell, while NA cleaves mature virus from the host cell (36, 37). There is evidence that HA- and NA-targeting antibodies exert their activity via different mechanisms, and while HA antibodies are able to prevent influenza virus infection, NA antibodies are infection-permissive but may reduce disease severity (38).

Mutations in the HA and NA surface glycoproteins occur naturally during viral replication, sometimes resulting in different antigenic properties (39, 40). Antigenic drift involves small changes to HA and NA that commonly accumulate over time and may result in viruses that are antigenically different and no longer as well recognised by antibodies that were generated in response to infection by previous influenza strains or vaccination; over time, this leads to reduced protection from previously acquired immunity. Antigenic drift occurs in both influenza A and influenza B viruses (41-44) and has the potential to lead to epidemics. Antigenic shift due to reassortment may also occur in influenza A virus and comprises a major and abrupt change in the genes encoding HA and/or NA (45, 46). For example, a new influenza A (H1N1) virus (S-OIV) emerged in 2009 with genes from viruses originating from North American and Eurasian swine, humans and birds, causing a pandemic (47). If shifts are sufficiently large, and involve subtypes which are novel in humans, they can result in a new influenza A subtype for which the population has limited or no immunity, thus causing pandemics (43, 44). It is also theoretically possible that a pandemic influenza virus might emerge in the future by gradual adaptation of a novel non-human subtype to humans.

History of the development of influenza virus vaccines

Vaccination remains the most effective public health intervention for prevention of influenza virus infection (48, 49) and its associated complications (50, 51). Influenza A virus (strain H1N1) was first isolated in 1933 and, in 1935, the virus was subsequently grown in fertilised chicken eggs (52, 53). The first influenza virus vaccine, developed in 1938 (Fig. 2), was an inactivated preparation containing a single influenza type A strain, termed a monovalent vaccine. The influenza B virus was subsequently discovered in 1940 (54) and, in 1942, an inactivated bivalent vaccine containing influenza types A and B was developed (52). In 1977, the re-emergence of influenza A strain H1N1 (55, 56) prompted the World Health Organization (WHO) in 1978 to recommend a trivalent vaccine (against the H1N1 and H3N2 strains of influenza A, and a type B virus) to ensure effective protection (57). In the 1980s, antigenic drift led to the circulation of two antigenically distinct lineages of influenza B virus

(58). The trivalent vaccine offered little to no protection against the circulating influenza B virus in five of the 10 seasons between 2001 and 2011 (58-60). This necessitated a quadrivalent inactivated influenza virus vaccine (QIIV), which was subsequently developed and first approved in 2012, protecting against two influenza A (H1N1 and H3N2) and two influenza B virus strains (B-Victoria and B-Yamagata lineages) (61). Changes in circulating subtypes have continued and there have been no confirmed cases of influenza B-Yamagata detected since March 2020 (62), and in 2023 the WHO recommended a return to trivalent vaccines, omitting the B-Yamagata strain (63, 64). Given that vaccines are only effective against circulating virus strains and B-Yamagata is no longer in circulation, removal of this strain from the QIIV vaccine is unlikely to impact the effectiveness of the resulting trivalent inactivated influenza virus vaccine (TIIV). This timeline highlights that the dynamic nature of influenza and needs to be considered in the approach to vaccination (Fig. 2).

WHO recommendations on strain selection

The antigenic shift and drift of influenza viruses necessitates regular updates to the composition of seasonal vaccines to remain effective. Each year, the WHO makes recommendations on the viral composition of influenza virus vaccines for both the Northern (October to February) and Southern hemisphere (September to January) influenza seasons. These recommendations are made 6 months ahead of the respective seasons and are based on surveillance data generated by the WHO Global Influenza Surveillance and Response System (49, 64). Designated national influenza centres around the world, send isolated viruses for genetic and antigenic characterisation to WHO collaborating centres, including the Francis Crick WHO collaborating centre in the UK (65), and data from these centres are used to inform the recommendations on the composition of the influenza virus vaccine required for protection in the next season (64, 66, 67).

In the UK, national surveillance is conducted by the UK Health Security Agency (UKHSA), which collates and interprets data providing information on both influenza activity and

estimates of all-cause mortality (9). Surveillance conducted during each influenza season also permits estimates of vaccine effectiveness (68-70), which can inform local recommendations (71).

National immunisation programmes

Most national influenza policies recommend vaccinating specific populations at increased risk of influenza-related complications (15, 72, 73). Recommendations across National Immunisation Technical Advisory Groups (NITAGs) continue to evolve as vaccine technologies develop and vary somewhat between countries in terms of the ages and populations to be vaccinated, as well as vaccine types and dosages (71, 74-76). Differences in recommendations derive from the characteristics of available vaccines, clinical data, and local surveillance data used, as well as affordability and cost-effectiveness criteria (77).

To ensure that NITAG policy recommendations are consistent and transparent, the WHO recommends the use of a systematic, standardised decision-making process (78). The quality of evidence should be assessed using methods such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) (79), although it is not known whether all countries implement this approach.

In the UK, recommendations for population level vaccination are made by the Joint Committee on Vaccination and Immunisation (JCVI) which reviews the criteria for a clinical risk group requiring influenza virus vaccination (11, 76). Since 2000, the list of clinical risk groups has been extended (Fig. 2) (11), as have the age groups of children who are eligible for routine annual influenza virus vaccination (Fig. 2) (76, 80-84).

Vaccines for pandemic preparedness

The WHO has a framework in place to improve preparedness for pandemic influenza, which leverages the capabilities of existing systems for seasonal influenza (85). Several countries have advance purchase agreements for pandemic-specific influenza vaccines, including the UK, USA and Australia (86-88). The mRNA platform will be a key part of the pandemic

vaccine response due its ability to facilitate the rapid incorporation of new antigens, as demonstrated during the COVID-19 pandemic (89, 90). The influenza A virus subtype H5N1 is now enzootic in wild aquatic birds and is a severe, highly infectious influenza virus in susceptible avian species (85, 91). The increased genetic exchange among influenza viruses in wild aquatic birds, commercial and domestic poultry, pigs and humans, poses a continuing threat to humanity (85). Public health concerns have recently been heightened by the spillover of the novel highly pathogenic avian H5N1 influenza virus HA clade 2.3.4.4b into dairy cattle, where it appears to be transmitting via the milk (92-95). There have been cases of interspecies transmission to humans (93, 96-98) and the situation is being continuously monitored by health authorities worldwide (99-102). Although there is current interest in pandemic vaccines, particularly with respect to the influenza A H5N1 virus, this is outside the scope of this review and has been assessed in a recent review article (103).

Influenza virus vaccine technologies

From the 1940s to the 2010s, inactivated influenza virus vaccine (IIV) technology remained largely unchanged and consisted of inactivated viruses grown in embryonated chicken eggs (52). Influenza virus vaccines produced using egg-based technology have been available in the UK since the 1960s. Egg-based technology remains the most commonly used influenza virus vaccine production method worldwide, largely due to availability, manufacturing capability and scalability, low costs, and historical use, with safety and tolerability data collected over 50 years (104). However, technological advances in the past two decades have enabled the development of alternative technologies for manufacturing influenza virus vaccines, designed to overcome certain limitations of the standard egg-based vaccines. At present, there are six different influenza virus vaccine types available in the UK, five of which are manufactured using different technologies to that of the standard-dose egg-based IIVs (adjuvanted QIIV, cell-based QIIV, high-dose QIIV, live-attenuated influenza virus vaccines [LAIV] and recombinant QIIV) (105-111). Although these technologies have been previously described to varying extents (104, 112-116), there is no recent published comprehensive and

detailed summary of the technologies and characteristics, alongside clinical data. The following sections represent the first comprehensive summary of advances in the influenza virus vaccine landscape, describing vaccine technologies in use in the UK and more widely, and reviewing associated clinical data.

METHODOLOGY

Literature searches

We conducted a literature search in the PubMed database and Cochrane Library covering a ~six-year period from 01/01/2018 to 15/07/2024, limited to English language articles. The initial date of 2018 was chosen as this is when the enhanced influenza virus vaccines (i.e. those other than standard-dose egg-based influenza virus vaccines) became available in the UK and were recommended more consistently compared with standard-dose egg-based vaccines in other countries. The full search strategy, including search terms (Table S1) and the eligibility criteria for article selection (Table S2), is described in the supplemental materials. Filters were applied to include only randomised controlled trials (RCTs), systematic reviews, and meta-analyses. Articles were included if they described clinical studies investigating the efficacy or effectiveness of influenza virus vaccines with reported clinical outcomes such as (but not limited to) laboratory-confirmed influenza virus infection (a documented positive influenza test by viral culture, fluorescent antibody assay, reverse transcription-polymerase chain reaction, or a rapid influenza diagnostic test), influenza-like illness (ILI), or influenza-related hospitalisation. There is no standard, international definition of ILI; the majority of studies in this review defined ILI as clinical diagnosis based on symptoms such as headache, high temperature, cough, and muscle pain. The WHO define ILI as an acute respiratory infection with onset within the past 10 days, presenting with cough and a measured temperature of ≥38°C (117), and the Centers for Disease Control and Prevention (CDC) as fever ≥37.8°C and cough and/or sore throat (118).

Although immunogenicity data are a main criterion for annual re-licensure, they are not described here due to the lack of global standardisation for measuring protective immune response using methods such as haemagglutination-inhibition assays (119), and uncertainties related to correlation with clinical protection (120, 121). Some studies have examined the impact of influenza virus vaccines on conditions more broadly associated with influenza, e.g. cardiovascular disease (122-130), but these are not included as the focus of the review was respiratory infection and disease. As the safety profiles of influenza virus vaccines have been well established (49, 131), these data are not included in the results tables but are instead discussed in the text.

Seasonal influenza virus vaccines were included in the review and grouped based on the following technology:

- IIVs produced using egg-based technology (further sub-divided into standard dose, adjuvanted and high-dose)
- LAIVs
- Recombinant influenza virus vaccines
- IIVs produced using cell-based technology.

A summary of the studies selection strategy is reported in the flowchart in the supplemental material (Fig. S1). PubMed database and Cochrane Library searches returned a total of 278 publications, and an additional four publications that met the inclusion criteria were identified in a separate ‘manual search’ (Fig. S1). After applying the exclusion criteria, 41 articles were selected for inclusion in this review (Table 2–7) (131-171). A narrative approach was taken to data synthesis.

Summary of evidence

For each vaccine technology, a brief history of the development is given, followed by the key characteristics, and a summary of the available clinical outcome data. Where available, data for absolute and/or relative vaccine efficacy and effectiveness are summarised. Efficacy and

effectiveness are distinct concepts related to the therapeutic performance of a vaccine (172). Vaccine efficacy is measured under strictly controlled conditions, using RCTs; whereas vaccine effectiveness explores the performance of a vaccine in a real-world setting, generally using observational methods (173). Whilst observational studies have advantages, there is an inherent risk of bias; to mitigate this, studies that use randomisation in real world settings may be implemented.

OVERVIEW OF VACCINE TECHNOLOGIES

Manufacturing influenza virus vaccines: egg-based technology

Egg-based vaccine manufacturing is used to produce IIVs and LAIVs, by classic genetic reassortment. This involves coinfection of the WHO candidate virus with either a selected high-growth virus (capable of replicating at high titres in eggs and cells) for IIV, or a master donor attenuated virus for LAIV, into embryonated chicken eggs (174). Appropriate seed viruses are then selected by amplification in the presence of antibodies against the HA and NA of the high-growth virus or the master donor virus. The resulting viruses are used for vaccine production (Fig. 3) (174). This egg-adapted vaccine strain virus is then mass produced before undergoing purification and formulation (174).

The manufacturing of egg-based vaccine depends on the availability of embryonated chicken eggs and the ability of influenza viruses to propagate in eggs, and it is both time and biosecurity-intensive (Fig. 3) (174, 175). In particular, the manufacturing process requires a prolonged process of planning and execution and can take several months (and usually a minimum of 4–6 months) (175, 176). Some influenza virus strains (especially avian strains such as H5N1) negatively impact egg production (177), therefore the use of this technology may be unsuitable for the production of large titres required in pandemics. Furthermore, egg-based production can be affected by ‘egg-adaptation’ of the influenza virus, resulting in changes to the antigenic structure of the HA protein (178-180). This egg-adaptation may result in antigenic differences between the antigens in the vaccine and the WHO

recommended strains. The phenomenon of antigenic mutations caused by egg adaptation is particularly prominent in H3N2 virus; a study found that, on passage of the virus up to 15 times in eggs, mutations occurred in three amino acid sequences in HA, two of which were located near the surface of the receptor binding site (179). Providing the WHO recommended strains match the circulating strains, this will reduce vaccine effectiveness as the immune response in humans may not be optimally focussed on the wild virus strain that was recommended by the WHO (181-183). The JCVI noted the issue of egg-adaptation as a 'real concern' but highlighted that its impact will likely be limited to influenza seasons in which H3N2 strains dominate (76). Egg-adaptation is more common in H3N2 viruses than in H1N1 (184), perhaps because the former have had longer to adapt to the human airway, becoming less like avian influenza viruses. When grown in eggs, human H3N2 viruses may acquire mutations in the receptor-binding site of HA in order to facilitate their growth, which can alter the antigenicity of HA (184). This, in turn, has been estimated to result in reductions in influenza absolute vaccine effectiveness by up to 16% (185). Despite these potential shortcomings, egg-based technology is well established, and has been used for decades to successfully support the delivery of influenza immunisation programmes.

Although studies have demonstrated that individuals who are allergic to eggs can safely receive egg-based vaccines (186, 187), these vaccines are not recommended in people with certain egg allergies (18). Healthcare professionals outside of the UK should consult their relevant local guidelines regarding the use of egg-based vaccines in egg-allergies individuals (49).

Standard-dose inactivated influenza virus vaccines (SD-IIVs)

Technology overview

There are three types of IIV: whole virion, split-virion, and subunit vaccines (Fig. 3). Whole vaccine inactivation is most commonly achieved through chemical modification; using formaldehyde or β-propiolactone, or physical manipulation by ultraviolet (UV) or gamma irradiation (188). Formaldehyde acts as a cross-linking agent; via this mechanism,

formaldehyde suppresses viral genome replication and initiates viral genome degradation, thereby reducing viral infectiousness (188). β-propiolactone acts mainly as a nucleic acid alkylating agent, inhibiting viral genome replication (188). UV radiation and gamma irradiation primarily cause destruction of the viral genome, interfering with viral replication and transcription in host cells. In split-virion vaccines, the viral envelope has been disrupted using a surfactant (189). The split-virion vaccine can be further purified to remove other viral components, such as the internal subviral core, to yield viral subunits containing HA and NA antigens (a subunit vaccine) (115). The current standard-dose of TIIV and QIIV formulations contain, in addition to the other viral components, a standardised 15 µg of HA per strain per dose (49).

Clinical data: efficacy and effectiveness

IIVs have shown efficacy in all age groups, including children and adolescents 6 months–17 years of age, adults ≥65 years of age and pregnant individuals (Table 2) (133, 135-139, 141, 142, 145, 146, 164-166). As egg-based SD-IIVs were the standard of care prior to development of newer technologies, historical comparisons of vaccine efficacy and effectiveness were predominantly made to placebo (e.g. saline), non-influenza virus vaccine control, or no vaccination (Table 2). Newer technologies may be compared with egg-based SD-IIVs.

A systematic review and meta-analysis that included 41 studies of children and adolescents 2–16 years of age showed that, compared with placebo or no vaccination, IIV treatment was associated with a 64% reduction in risk of laboratory-confirmed influenza (95% CI: 52, 72; N=1,628; high-certainty evidence), and reduced ILI by 28% (95% CI: 21, 35; N=19,044; moderate-certainty evidence) (Table 2) (165). In a systematic review and meta-analysis of 25 studies in healthy adults 16–65 years of age comparing IIV against placebo or unvaccinated control groups, the risk of laboratory-confirmed influenza was reduced by 59% (95% CI: 53, 64; N=71,221; moderate-certainty evidence) and risk of ILI was reduced by 16% (95% CI: 5, 25; N=11,924; low-certainty evidence) after IIV (Table 2) (164). Results from a Cochrane

review in adults ≥65 years of age demonstrated that IIV reduced the risk of laboratory-confirmed influenza over a single season by 58% compared with placebo (95% CI: 34, 73; N=2,217; low-certainty evidence), and the risk of ILI (subjective report) by 41% compared with those who were not vaccinated over a single influenza season (95% CI: 27, 53; N=6,894; moderate-certainty evidence) (Table 2) (166). In a pooled estimate from three RCTs, vaccine efficacy for QIIV, compared with control (placebo or a non-influenza [meningococcal ACWY] vaccine), against laboratory-confirmed influenza in pregnant individuals was 50% (95% CI: 32, 63) (Table 2) (142).

Clinical data: safety

Vaccination with IIV has some common adverse effects (AEs). Compared with placebo, IIV was associated with an increased risk of fever in adults ≥18 years of age (164) and increased risk of sore arm and swelling in adults ≥65 years of age (166). In a multinational RCT in children 6–35 months of age, the safety profiles were similar for QIIV, TIIV, and placebo, except for more frequent injection-site reactions with QIIV compared with placebo (138).

Although egg-based SD-IIVs are progressively less used in the UK, in some countries they are still utilised, particularly in younger cohorts, and are used in national immunisation programmes (190, 191). Indeed, SD-IIVs are now only recommended in the UK for individuals <65 years of age in the ‘at risk’ cohorts as a third-line option, in the event that the first- or second-line options recommended by the JCVI are simultaneously unavailable for vaccination (76).

High-dose inactivated influenza virus vaccines

Technology overview

Older adults (≥65 years of age) are affected by waning humoral and cellular immunity that occurs with aging, known as immunosenescence (192), which is thought to increase disease susceptibility and severity, and reduce responses to vaccination (192, 193). High-dose IIVs

are developed using the same egg-based technology as standard-dose egg-based vaccines, but contain in addition to the other viral components a higher dose of HA per strain (60 µg per strain rather than 15 µg). The higher doses of HA induce increased post-vaccination HA specific antibody titres and provide increased protection from influenza, which makes them particularly appropriate for use in older people (194-196).

Clinical data: efficacy and effectiveness

High-dose IIVs have demonstrated improved vaccine efficacy compared with SD-IIVs in terms of protection against laboratory-confirmed influenza or ILI (Table 3) (132, 150-152, 168, 169). In a meta-analysis of 21 studies that included data over 12 consecutive influenza seasons and among 45 million individuals of ≥65 years, high-dose TIIV demonstrated improved protection against laboratory-confirmed influenza or probable ILI compared with standard-dose TIIV/QIIV (relative vaccine effectiveness of 24.1%; 95% CI: 10.0, 36.1) (Table 3) (150). Similar results were reported for efficacy against laboratory-confirmed influenza in adults (including studies of adults ≥65 years of age and immunocompromised adults); high-dose TIIV was associated with a 24% (95% CI: 10, 36) reduction in risk compared with SD-TIIV (Table 3) (152). In a meta-analysis of five RCTs in adults ≥65 years of age, use of high-dose TIIV/QIIV was associated with reduced risk of hospitalisation due to pneumonia or influenza when compared with standard-dose TIIV/QIIV (pooled relative vaccine efficacy: 23.5%; 95% CI: 12.3, 33.2) (Table 3) (170).

Clinical data: safety

In a systematic review that included 36 studies of adults (≥18 years of age), high-dose IIVs were associated with higher rates of local and systemic AEs compared with SD-IIVs, including a higher frequency of headache, chills, and malaise (168).

Adjuvanted inactivated influenza virus vaccines

Technology overview

Adjuvanted IIVs are developed using the same egg-based technology as standard- or high-dose egg-based vaccines, but an adjuvant is added. Adjuvants are substances that enhance the magnitude, breadth, and durability of the vaccine-induced immune response via various signalling pathways, leading to enhanced chemokine and cytokine secretion and activation of immune cells (197, 198). Common vaccine adjuvants include alum, oil-in water emulsions (such as MF-59 and AS03), combinations of alum, emulsions, and/or liposomes, and toll-like receptor ligands (197). As with high-dose IIVs, the potential improved immunogenicity of adjuvanted versus non-adjuvanted vaccines makes them suitable for older adults who have waning humoral and cellular immunity (199).

Clinical data: efficacy and effectiveness

Results from a multicentre RCT in children 6 months to 5 years of age, over two influenza seasons (2013–2015), showed a MF59-adjuvanted vaccine (aQIIV) to be effective in preventing laboratory-confirmed influenza compared with IIV (TIIV or QIIV), in a 6–23 months subgroup (relative vaccine efficacy 31.37% [95% CI: 3.14, 51.38]), but not for the overall study population (age 6 months to 5 years), with a relative vaccine efficacy of –0.67% (95% CI: –19.81, 15.41) (Table 4) (153). This is perhaps because children younger than 2 years have immature immune systems that are known to respond relatively poorly to standard influenza vaccines. Evidence from a systematic review and meta-analysis of 48 studies demonstrated that adjuvanted standard-dose egg-based influenza virus vaccines were also effective at preventing laboratory-confirmed influenza among older adults (≥65 years of age) compared with no vaccination (absolute vaccine effectiveness of 45%; 95% CI: 23, 61; from five non-randomised intervention studies across three influenza seasons), and had similar relative vaccine effectiveness to their non-adjuvanted counterparts (Table 4) (167). However, a systematic review of 11 analyses from nine real-world evidence studies of adults ≥65 years of age, reported that adjuvanted trivalent vaccines were significantly more

effective at reducing influenza-related outcomes than non-adjuvanted standard-dose vaccines (relative vaccine effectiveness ranging from 7.5 to 25.6% for adjuvanted versus non-adjuvanted TIIVs, and from 7.1 to 36.3% versus non-adjuvanted QIIVs) (Table 4) (156).

Clinical data: safety

Adjuvanted vaccines have been associated with more frequent local and systemic AEs than non-adjuvanted standard-dose egg-based vaccines (153, 154, 167), including a higher frequency of arm pain/tenderness, fever, myalgia, and chills (153, 154, 167). This has also been observed with non-influenza virus vaccines (200, 201) and is likely related to the mechanism of action of the adjuvant (202).

Live-attenuated influenza virus vaccines

Technology overview

LAIVs use 'cold-adapted' viruses, produced by chemical mutagenesis or serial passage of influenza viruses in eggs at gradually lower temperatures to introduce mutations (203, 204). Because of the segmental viral genome of the influenza virus, it is possible to mix genetic material from different strains. In the case of LAIV, internal gene segments (PB1, PB2, PA, NP, M NS) from the attenuated cold-adapted strain are then combined with HA and NA of the target virus strains to create a reassortant vaccine virus (Fig. 3), which replicates efficiently at low temperatures (in the upper respiratory tract), but not at elevated temperatures (in the lower respiratory tract) (49, 104, 203). The specific combinations of HA and NA genes can affect the immunogenicity of the recombinant vaccine virus (205). The interplay between the vaccine virus and the innate immune response may shape the downstream adaptive response (206).

The design of LAIVs, to replicate at the lower temperatures in the upper respiratory tract, requires intranasal delivery. This method of delivery allows for ease of administration, making them more acceptable to children compared with an injectable vaccine (11), as they are likely to be associated with little or no pain. Compared with other routes of

administration, LAIV provides a broader response by involving both systemic and mucosal immune responses, additionally LAIV may also induce a strong influenza virus specific cellular response (206-210). The mucosal immune response induced by LAIV vaccination is mediated through mucosal Immunoglobulin A (IgA) directed at the HA surface glycoprotein (207, 211), with the HA-specific IgA response being greater than that induced by IIV (212). Inducing airway mucosal immune responses may be more protective than systemic immunity alone by preventing virus infection at the point of entry (213).

A major justification for the use of LAIVs in school children, particularly those in primary education, is that they can also provide herd immunity protecting adults and elderly adults in the surrounding population. This was observed after introduction of LAIVs in primary school age children, demonstrating the impact of LAIVs in reducing transmission (214). As LAIVs stimulate a weaker immune response in adults compared with children, possibly due to pre-existing immunity that prevents viral establishment (209, 215, 216), they are not currently recommended nor licensed for use in those >18 years age in the UK (76). However, LAIVs are licensed in the USA in adults ≤49 years of age (217). Due to the potential risk of infection from using live viruses for immunisation, LAIVs are not recommended for individuals who are immunocompromised (18).

Clinical data: efficacy and effectiveness

LAIVs have demonstrated efficacy in children from 6 months of age (Table 5) (131, 140, 141, 146-149, 165). Compared with placebo or no vaccination, LAIVs were shown to reduce ILI by 31% (95% CI: 20, 40) based on data from a systematic review of RCTs including 124,606 children 3–16 years of age (Table 5) (165). Another systematic review and meta-analysis of children <18 years of age who were vaccinated with trivalent LAIVs showed a 48% (95% CI: 18, 68) reduced risk of laboratory-confirmed influenza compared with TIIV (Table 5) (131).

Clinical data: safety

The results of two RCTs demonstrated that quadrivalent LAIV was well tolerated in children, with a similar AE profile to placebo (148), whilst in a Phase 3 RCT in children 3–17 years of

age, trivalent LAIV was associated with a significantly increased incidence of fever compared with placebo (147). In a systematic review and meta-analysis of children <18 years of age, the rate for systemic AEs was not significantly higher with quadrivalent or trivalent LAIVs compared with placebo and trivalent LAIV showed a significantly higher rate for at least one local AE compared with placebo (131).

Alternative platforms to egg-based technologies

Cell-based and recombinant influenza virus vaccines are alternative manufacturing platforms to traditional egg-based vaccines, which have been developed to address issues associated with egg-based vaccines described in the previous section (such as egg adaptation) that reduce vaccine effectiveness (Fig. 3) (108, 218-220). The key characteristics and the clinical data underpinning these technologies are described below.

Cell-based influenza virus vaccines

Technology overview

The manufacturing process for cell-based inactivated influenza virus vaccine uses mammalian cells, e.g. Madin-Darby canine kidney cells (MDCK), to propagate viruses (Fig. 3). Using this method, candidate vaccine viruses cultivated by the CDC are used to inoculate cultured mammalian cells and allowed to replicate (221, 222). The virus-containing fluid is then collected and the virus antigen is purified (221, 222).

There are several advantages to cell-based technologies over egg-based influenza technologies. For example, cell-based manufacturing uses a more flexible viral production in a cell culture bioreactor; and it has a more scalable technology, a reduced manufacturing time, and a process that unaffected by potential egg shortages (104). Furthermore, cell-based technologies largely overcome the issues of egg-adaptation seen with egg-based influenza manufacturing (223-225). However, cell-based mutations in the HA and NA protein occur less frequently than mutations in egg-based technologies (179, 226, 227). The majority of these mutations occur in either antigenic sites or the receptor-binding site, and, if

they occur, will therefore likely have a similar effect to that of egg-adapted mutations(179, 226, 227).

Clinical data: efficacy and effectiveness

Influenza virus vaccines produced using cell-based technologies have demonstrated efficacy for laboratory-based influenza both in children and adolescents (2–<18 years of age) and adults (≥18 years of age) (Table 6) (160, 161). In an RCT, a QIIV reduced the occurrence of laboratory-confirmed influenza by 54.6% (95% CI: 45.7, 62.1) in children and adolescents (2–<18 years of age) compared with a non-influenza (meningococcal ACWY) vaccine (160). A systematic review and meta-analysis of 19 studies reported, in data from two RCTs, that the overall absolute vaccine efficacy of trivalent, cell-based vaccines for preventing laboratory-confirmed influenza was 70% (95% CI: 61, 77) in adults (≥18 years of age) versus no vaccination (Table 6) (161). Furthermore, in a systematic review and meta-analysis of real-world evidence studies among individuals ≥4 years of age, the absolute vaccine effectiveness of a QIIV for preventing laboratory-confirmed influenza across five pooled studies was estimated to be 37.6% (95% CI: 19.4, 55.9) vs 26.1% (95% CI: 6.7, 45.4) for egg-based TIIV/QIIV (162).

Clinical data: safety

A systematic review found that cell-based influenza virus vaccines were associated with significantly higher rates of bruising than traditional egg-based IIV; rates of other local reactions (pain, redness, swelling, and induration) were similar between the two vaccine groups (161).

Recombinant influenza virus vaccines

Technology overview

In contrast to egg-based or cell-based influenza virus vaccines, the antigens contained in a recombinant influenza virus vaccine are expressed directly from a genetic sequence using recombinant protein technology (222, 228, 229); neither chicken eggs nor a candidate

vaccine virus are required for production (Fig. 3). For the recombinant influenza virus vaccine, an established manufacturing platform for the production of viral vaccines and gene therapy vectors, the baculovirus expression vector system is used (228-230). First, the influenza HA gene is cloned into the baculovirus genome using homologous recombination (230). The resulting recombinant baculovirus is then transfected into insect cells (228-230).

Once a host insect cell line is transfected by the recombinant baculovirus, it instructs the cells to rapidly produce the HA antigen (Fig. 3). As the HA antigen is expressed directly from a genetic sequence, rather than derived from the replication of influenza viruses in eggs or mammalian cells, potential egg-adaptive and cell-adaptive mutations from the manufacturing process of recombinant vaccines are avoided (229). Therefore, the expressed HA antigen is genetically identical to a chosen influenza strain, e.g., the seasonal strain recommended by the WHO. The recombinant vaccine currently available contains only HA at a concentration three times higher than standard-dose egg-based vaccines (45 µg) which, together with restriction of mutations, may have contributed to a higher vaccine efficacy than a standard-dose-egg-based QIIV, as demonstrated in clinical trials (228).

Production of influenza virus vaccines using recombinant technologies takes less time (2–3 months) than with egg-based vaccines (175), and recombinant vaccines do not require additional inactivation steps. Furthermore, unlike egg-based vaccines, recombinant vaccines contain no trace egg proteins, antibiotics, or preservatives (229), making them suitable for all people with egg allergy, including those who have experienced severe egg anaphylactic reactions.

Clinical data: efficacy and effectiveness

One study identified in a systematic review (158) found that a recombinant TIIV demonstrated a 45% (95% CI: 19, 63) relative vaccine efficacy, compared with placebo, against laboratory-confirmed influenza in adults 18–55 years of age (Table 7) (231). Another RCT from this systematic review found that a recombinant QIIV had a higher relative vaccine efficacy in preventing laboratory-confirmed influenza compared with a standard-dose egg-

based QIIV among adults ≥50 years of age (relative vaccine efficacy of 30%; 95% CI: 10, 47; one RCT, moderate-certainty evidence Table 7) (158). In a systematic review and network meta-analysis of 41 RCTs, recombinant TIIVs/QIIVs had a vaccine efficacy of 70.6% (95% CI: 22.9, 90.2; nine RCTs) against laboratory-confirmed influenza when compared with placebo (Table 7) (169). Findings from a cluster-randomised observational study demonstrated a relative vaccine effectiveness against laboratory-confirmed influenza of 15.3% (95% CI: 5.9, 23.8) for recombinant QIIV versus a standard-dose egg-based vaccine in adults 50–64 years of age (Table 7) (171).

Clinical data: safety

A systematic review and meta-analysis demonstrated similar rates of fatigue, headache, myalgia, or nausea between a recombinant influenza virus vaccine and traditional QIIV (158) but a significantly higher rate of chills with the recombinant vaccine (158). There were significantly fewer local reactions, including pain, erythema, swelling and tenderness, with the recombinant vaccine compared with IIV (158).

FUTURE VACCINE TECHNOLOGIES

Introduction

The main focus of this review article is on the clinical data supporting the development of the six influenza vaccine types currently available in the UK. However, in this final section we present a brief overview of future influenza virus vaccine technologies. The development of the previously described ‘new’ technologies for influenza virus vaccines, as well as an increased antigen dose, has provided valuable improvements for influenza prevention compared with standard-dose egg-based technologies. Not all vaccine technologies have been investigated for clinical outcomes (i.e. influenza virus infection or hospitalisations) in head-to-head randomised efficacy trials in which the comparator is the standard of care, standard-dose egg-based vaccines. However, for those vaccine technologies that have been investigated in this way, vaccine efficacy for the prevention of laboratory-confirmed influenza,

relative to standard-dose egg-based vaccines, still remains moderate overall, estimated at up to 30% (95% CI: 10, 47) in adults (Tables 3–7) (131, 152, 157, 158, 163). The overall effectiveness of influenza virus vaccines remains largely below that of vaccines for other vaccine-preventable infectious diseases. For example, vaccine effectiveness is >90% for vaccines that prevent measles infection (232), and is up to 100% for the prevention of meningococcal disease with meningococcal C conjugate vaccines (233). In comparison, vaccine effectiveness against all laboratory-confirmed influenza presenting within primary care in the UK is 49% (95% CI: 42, 56) in adults 18–64 years of age and 46% (95% CI: 29, 59) in adults ≥65 years of age (234). Vaccine effectiveness against influenza-related hospitalisation in England could also be improved, with vaccine effectiveness of 54% (95% CI: 42, 63), 31% (95% CI: 21, 40) and 30% (95% CI: 22, 37) in individuals 2–17 years, 18–64 years and ≥65 years of age respectively (vaccine effectiveness data in Scotland are grouped with other respiratory conditions, and are not available for Wales and Northern Ireland) (234). Similar influenza virus vaccine effectiveness has been reported in the US, with 33% (95% CI: 16, 47) to 49% (95% CI: 47, 51) against laboratory-confirmed influenza in outpatient settings and 41% (95% CI: 34, 47) to 44% (95% CI: 32, 54) against influenza-associated hospitalisation (235). Therefore, there remains an unmet need for the development of additional technologies that may overcome some of the shortcomings associated with current technologies and improve influenza virus vaccine efficacy. Here we present a short overview of various technologies that are currently being developed or are in pre-licensure clinical trials.

Nucleic acid technologies, viral vectors, and virus-like particles

Technology overview: nucleic acid technologies

Vaccines based on nucleic acids (DNA and RNA) have been in development since the 1990s, and offer considerable potential to overcome limitations of established vaccine platforms (236-238). DNA vaccines differ from the previously discussed recombinant vaccines in that they deliver DNA, rather than recombinant antigen (229, 236, 238). In 2021,

a DNA plasmid-based SARS-CoV-2 vaccine (ZyCoV-D) was approved in India for active immunisation to prevent COVID-19 in individuals ≥12 years of age (239-241), suggesting that the technology may be appropriate for other respiratory infectious diseases, such as influenza.

The mRNA contained within mRNA-based vaccines encodes the viral protein that elicits the immune response (Fig. 3) (242). Processes involved in the production of mRNA vaccines vary, but typical steps are as follows: the antigen of interest is sequenced, and the optimised consensus sequence is used to create a linearised plasmid DNA template, which is then amplified and purified (242-244). This DNA template is then used as the basis for synthesis of the target mRNA for the antigen by RNA polymerase enzymes (245). Finally, purified mRNAs are encapsulated into a lipid nanoparticle (LNP) for delivery (246). A critical step for mRNA vaccine immunogenicity and efficacy is the incorporation of modified nucleotides (247), which can reduce the cell intrinsic response to the mRNA itself (248).

mRNA-based vaccines offer several benefits over traditional technologies, including a short manufacturing time that would accelerate production and availability of a vaccine, particularly during a pandemic (249-252). Furthermore, shorter manufacturing times could mean that mRNA vaccines are developed closer to the start of an influenza season to reduce time-lag and the potential for antigenic mismatch before or in-season, though there would also be considerations regarding rapid licensure and distribution.

Clinical data

A number of DNA influenza virus vaccines are being investigated in Phase 1 clinical trials (253-259). The results from a Phase 1 study of pandemic H1 DNA vaccine showed it was well tolerated in healthy adults (24–70 years of age) (254). The H1 DNA vaccine demonstrated modest immunogenicity when administered as a single agent (prime vaccination) (254). DNA vaccines may also offer a potential strategy to improve immunogenicity of current influenza virus vaccines, as evidenced in studies with influenza

DNA vaccine prime followed by inactivated vaccine boost (258, 259). In a Phase 1 clinical trial, H5 DNA priming followed by administration of a monovalent inactivated vaccine boost ≥12 weeks later, resulted in 4-fold increases in haemagglutination inhibition (HAI) titre in 91% of recipients (258).

Several mRNA influenza virus vaccine candidates are currently being investigated (260-272). Final results of a Phase 1/2 clinical trial in healthy adults ≥18 years of age demonstrated that a quadrivalent mRNA vaccine against seasonal influenza, mRNA-1010, at 25–100 µg has a higher immunogenicity for influenza A virus and similar immunogenicity for influenza B compared with SD-IIV through 6 months after vaccination (273). Lower doses of mRNA-1010 elicited generally higher (12.5 and 25 µg) or comparable (6.25 µg) titres to SD-IIV for influenza A virus strains, but lower for influenza B strains (273). Solicited adverse reactions were more common with mRNA-1010 than with a licensed, seasonal QIIV and were typically grade 1 or grade 2 in severity (273). Phase 3 trials to assess the safety and efficacy of mRNA-1010 are ongoing (260, 261).

Two Phase 1, randomised, placebo-controlled, double-blind, clinical trials were conducted to evaluate the safety and immunogenicity of the first mRNA vaccines against avian H10N8 and H7N9 influenza viruses, which have the potential to cause a pandemic (274). The vaccines were well tolerated and elicited robust humoral immune responses in healthy adults (274). Future studies investigating different valences will need to assess the tolerability of larger doses of RNA vaccines to determine whether multiple antigens can be delivered.

Technology overview: viral vectors

Viral vector vaccines contain genomes that have been modified with genes encoding target antigens from specific pathogens (275). The advantages of viral vectors include the ability to elicit both antibody and cellular responses, the latter of which is important for the elimination of pathogen-infected cells, and the ability to induce long-lasting immune responses (276). Viral vector vaccines offer similar advantages to mRNA vaccines, including the ability to

replace the HA cassette rapidly. However, there are potential challenges of anti-vector immunity, especially with repeat immunisations (275, 277).

Clinical data

Results from a Phase 1 study to evaluate the safety and immunogenicity of an adenovirus vector encoding the HA gene of H1N1 influenza, showed a 4-fold increase in HAI titres in 83% of the participants after booster vaccination (278). Phase 1–3 clinical studies have been conducted for other infectious diseases (279), including Phase 3 trials for chimpanzee adenovirus ChAdOX1 as a delivery vector for the coronavirus S gene, achieving 70% (96% CI: 55, 81) efficacy against virologically-confirmed COVID-19 (280). Further clinical trials of viral vector influenza vaccines in humans should provide insight into whether this approach will be more effective than conventional vaccines.

Technology overview: recombinant virus-like particles (VLPs)

Another new technology currently in development for influenza virus vaccines is recombinant VLPs prepared in mammalian, insect, and plant expression systems (281-283). The biological and morphological characteristics of recombinant VLPs are similar to the wild-type influenza virus (284), thus avoiding the drawbacks associated with antigenic drift. VLPs consist of a viral capsid without the core viral RNA required for replication (284). Therefore, although VLPs contain immunological epitopes and are highly immunogenic, they are not infectious (284).

Clinical data

Multimeric-001 is a vaccine formulated with conserved linear epitopes derived from influenza type A and type B proteins that play pivotal roles in viral infection (285). Results from a Phase 2, randomised, double-blind placebo-controlled trial in healthy adults showed that Multimeric-001 induced a polyfunctional CD4+ T-cell response that persisted through 6 months of follow-up (286). In two Phase 3 RCTs, a plant-derived VLP influenza virus vaccine demonstrated substantial protection against ILI compared with placebo in adults (283). In the study with adults 18–64 years of age, the primary endpoint of 70% absolute vaccine efficacy

to prevent laboratory-confirmed influenza with respiratory illness for the VLP vaccine versus placebo was not met (35.1% [95% CI: 17.9, 48.7]). The study in adults ≥65 years of age met its primary non-inferiority endpoint of prevention of ILI; relative vaccine efficacy of the VLP vaccine versus an inactivated vaccine control was 8.8% (95% CI: −16.7, 28.7) (283).

Bi- and tri-pathogen immunisation strategies

Combination vaccines reduce the number of injections required to protect against multiple diseases and may increase adherence to immunisation schedules (287). Combination vaccines, for example DTaP (diphtheria, tetanus toxoid, and acellular pertussis) and MMR (measles, mumps, and rubella) have long been available (287). More recently, following two Phase 1/2 RCTs conducted to investigate a combination of both influenza and COVID-19 vaccine components in an mRNA vaccine (288, 289), a Phase 3 trial successfully demonstrated greater efficacy at eliciting an immune response against both viruses in adults ≥50 years of age compared with vaccines that targeted only one (290, 291). Future developments may also include combination vaccines that offer protection from influenza, COVID-19, and respiratory syncytial virus (RSV) in a single formulation (287). Decisions regarding the strains of SARS-CoV-2 and influenza virus to be included in combination winter vaccines should be coordinated to optimise production.

Potential for a universal influenza virus vaccine

The risk of antigenic reassortment leading to a reduction in vaccine effectiveness necessitates regular surveillance of circulating influenza viruses and reformulation of vaccines each influenza season (292-295). Predicting the circulating influenza strain for future influenza seasons is difficult and antigenic mismatch sometimes occurs. Furthermore, there is always a risk of emergence of a pandemic influenza virus, either as a result of new, pathogenic reassortants or zoonotic events in which highly pathogenic avian influenza viruses, such as H5N1, H7N9 and H9N2, are transmitted to humans (with additional genetic

changes facilitating human-to-human transmission) (296). Following such events, current vaccines would likely offer little or no protection in an ensuing pandemic.

As such, there is a need for the development of ‘next-generation’ universal influenza virus vaccines, to protect against a wide variety of influenza subtypes – including both drifted or heterologous seasonal influenza virus strains, and new emerging strains that could potentially lead to a pandemic. Several candidate universal influenza virus vaccines are in clinical development (297). One approach is to introduce new antigenic targets related to highly conserved and stable epitopes of the influenza virus HA stem domain, as opposed to the highly variable HA head (296, 298). As well as broadening protection, targeting conserved epitopes for vaccination may also increase the duration of protection. Other universal vaccine technologies include chimeric HA vaccines, which have shown the potential to provide broad protection against influenza viruses in a Phase 1 RCT (299).

A design of vaccines that are not pathogen specific was recently proposed using a concept termed ‘integrated organ immunity’ (300). This involves innate and adaptive immune systems and non-haematopoietic cells interacting in tissue to elicit lasting, antigen-agnostic immunity (300).

CONCLUDING REMARKS

With an estimated 15,000 excess deaths reported in England alone in the 2022/23 UK influenza season, mostly among adults ≥65 years of age (9), effective influenza prevention may impact the disease burden and associated healthcare costs (301). Seasonal influenza virus vaccination is effective at preventing illness and reducing severity of the disease (48, 49, 302), and influenza virus vaccines have been widely used for over 60 years for the immunisation of high-risk population subgroups (11). Most vaccines are manufactured using egg-based inactivated influenza technology but over the past decade, advances in vaccine technologies have seen the licensure of different technologies, resulting in improved immunogenicity and efficacy in certain patient subgroups. This is the result of many decades

of research and development, which is still ongoing, testing new and existing formulations and platforms to develop the most effective influenza virus vaccinations. This is of particular importance in certain population groups at risk due to underlying conditions, especially those with immunosenescence where the protective responses induced by seasonal influenza virus vaccination are blunted (192, 193). In the UK, non-adjuvanted egg-based vaccines have now been relegated to reserve use, only if there are shortages of primary recommended products (76).

Each influenza virus vaccine technology has its own advantages and constraints regarding manufacturing time and cost, influenza strain selection and matching to the seasonal circulating strains, cell- and egg-adaptation leading to mutations of grown viruses, and immunogenicity and reactogenicity profiles. We have summarised key aspects relating to each influenza virus vaccine technology and reviewed the associated clinical data. Despite the advances in technology, there remains an unmet need for influenza virus vaccines that are effective against multiple circulating strains; such vaccines would maximise population protection.

There are some limitations to our review. The inclusion criteria for the literature search focused specifically on RCTs, systematic reviews, and meta-analyses, and so the data reviewed and summarised are biased towards these forms of evidence. Therefore, real-world studies were not included in the literature search. Importantly, however, several systematic reviews and meta-analyses in our search included real-world studies (132, 140, 150, 155-157, 162, 163, 185). In addition, there may have been studies published after the search period for our literature search that have therefore been omitted from this review. However, to our knowledge this is the first comprehensive review of the new influenza virus vaccine technologies, situated against the clinical efficacy and effectiveness data, relating to influenza virus infections and hospitalisations. As such, the review should provide a useful resource for those interested in understanding more about advances in influenza virus vaccination.

The introduction of new influenza virus vaccine technologies highlights the need for robust and consistent methods to assess the performance of influenza virus vaccinations and immunisation programmes, particularly in relation to vaccine effectiveness, which may have a substantial impact on public health and on healthcare systems. It is important that national guidelines follow evidence-based criteria for the assessment of influenza virus vaccine effectiveness, taking into account the robustness of study designs. Recent developments in standardised immunological assays and identification of new immune markers as correlates of clinical protection need to be translated into vaccine development, so that pandemic vaccines are not reliant strain matching, a process that may take approximately 6 months, and can result in substantial morbidity and mortality before vaccine availability (120, 121).

The recent step change in influenza virus vaccination technologies that are recommended in the UK was motivated by the substantial public health burden of influenza at both a patient and a population level. Ongoing assessment of comparative (product-specific) and programmatic vaccine effectiveness, using robust methodologies, will facilitate recommendation of the most effective vaccines. Continued investment in research and development and demonstration of clinical efficacy of new and existing vaccine technologies will further enhance the existing UK vaccination programme.

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CONFLICTS OF INTEREST

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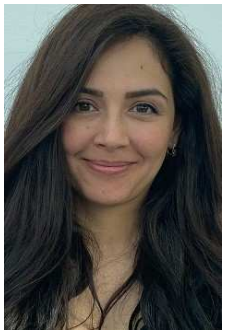

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FIG 1 Influenza samples analysed by GISRS for the WHO European Region from the 2016/2017 to the 2022/2023 influenza seasons (7).

Data are from FluNet (https://www.who.int/tools/flunet) (7). Changes have been made to the style and format of the figure in accordance with the license (https://creativecommons.org/compatiblelicenses).

GISRS, Global Influenza Surveillance and Response System; WHO, World Health Organization.

FIG 2 History of the development of influenza virus vaccines and development of the UK immunisation programme.

Eligibility was introduced for healthy adults in 2020 in the UK, but was removed in 2023 in England, Wales and Northern Ireland (they remain in Scotland at time of publication).

*Patients in clinical risk groups include those with chronic respiratory disease, chronic heart and vascular disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes/adrenal insufficiency, immunosuppression, asplenia/splenic dysfunction and morbid obesity. Patients who are carers or are household contacts of an immunocompromised individual may also be eligible. (Reference: Green book [Table 19.4]).

BMI, body mass index; EU, European Union; US, United States; WHO, World Health Organization.

FIG 3 Overview of egg-based, cell-based, recombinant, and mRNA vaccine technologies.

DNA, deoxyribonucleic acid; HA, haemagglutinin; mRNA, messenger ribonucleic acid; WHO, World Health Organization.

TABLE 1 Risk groups who should be offered influenza vaccination according to UK government guidelines (11).

Clinical risk category	Examples (this list is not exhaustive and decisions should be based on clinical judgement).
Chronic respiratory disease	Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children who have previously been admitted to hospital for lower respiratory tract disease.
Chronic heart disease and vascular disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease. This includes individuals with atrial fibrillation, peripheral vascular disease or a history of venous thromboembolism.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis.
Chronic neurological disease	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological or neuromuscular disease (for example polio syndrome sufferers). Clinicians should offer immunisation, based on individual assessment, to clinically vulnerable individuals including those

	with cerebral palsy, severe or profound, and multiple learning disabilities (PMLD), Down's syndrome, multiple sclerosis, dementia, Parkinson's disease, motor neurone disease and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.
Diabetes and adrenal insufficiency	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet-controlled diabetes. Addison's disease, secondary or tertiary adrenal insufficiency requiring steroid replacement.
Immunosuppression	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, people living with HIV (at all stages), multiple myeloma or genetic disorders affecting the immune system (for example IRAK-4, NEMO, complement disorder, SCID). Individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-TNF alemtuzumab, ofatumumab, rituximab, patients receiving protein kinase inhibitors or PARP inhibitors and individuals treated with steroid sparing agents such as cyclophosphamide and mycophenolate mofetil. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20 mg or more per day (any age), or for children under 20 kg, a dose of 1 mg or more per kg per day.

	Anyone with a history of haematological malignancy, including leukaemia, lymphoma and myeloma, and those with systemic lupus erythematosus and rheumatoid arthritis, and psoriasis who may require long term immunosuppressive treatments. Some immunocompromised patients may have a suboptimal immunological response to the vaccine.
Asplenia or dysfunction of the spleen	This also includes conditions such as homozygous sickle cell disease, hereditary spherocytosis, thalassaemia major and coeliac syndrome that may lead to splenic dysfunction.
Morbid obesity (class III obesity)*	Adults with a Body Mass Index ≥40 kg/m².

* Many of this patient group will already be eligible due to complications of obesity that place them in another risk category.

Adapted from Green book chapter 19 (11) under the version 3.0 of the Open Government Licence.

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TABLE 2 Overview of studies included in the review – standard-dose inactivated influenza virus vaccines.

Citation/reference	Evidence type / study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)*	Key effectiveness result(s)*
Infants ≤6 months of age							
Jarvis et al. 2020 (133)	Meta-analysis of two RCTs from a systematic review of RCTs and observational studies published up to Oct 2019	IIV	Placebo (saline)	Infants ≤6 months of age following maternal influenza virus vaccination (N=5742)	Laboratory (PCR)-confirmed influenza	Pooled VE of 34% (95% CI: 15, 50)	N/A
Children and infants ≥6 months of age							
Claeys et al. 2018 (139)†	Multinational RCT in five independent cohorts across influenza seasons from 2011 to 2014	QIIV	Non-influenza virus vaccine	Children 6–35 months of age (N=12,018 vaccinated)	Laboratory (RT-PCR)-confirmed influenza	VE was 64% (97.5% CI: 53, 73) against moderate-to-severe influenza and 50% (97.5% CI: 42, 57) against all influenza (regardless of disease severity)	N/A
Danier et al. 2019 (137)†	Exploratory analysis of a multinational RCT in five independent cohorts across influenza seasons from 2011 to 2014	QIIV	Non-influenza virus vaccine	Children 6–35 months of age (N=12,018 vaccinated)	Laboratory (RT-PCR)-confirmed influenza	Moderate-to-severe illness was 41% less likely (crude odds ratio 0.59 [95% CI: 0.44, 0.77]) and fever >39°C	N/A

						was 46% less frequent (crude odds ratio 0.54 (95% CI: 0.39, 0.75)	
Dbaibo et al. 2020 (135)[†]	Multinational RCT in five independent cohorts across influenza seasons from 2011 to 2014	QIIV	Non-influenza virus vaccine	Children 6–35 months of age (N=12,018 vaccinated)	Laboratory (RT-PCR)-confirmed influenza	VE across the five seasonal cohorts was 57.8% (95% CI: 40.2, 70.8), 52.9% (95% CI: 31.2, 68.3), 73.4% (95% CI: 61.7, 82.0), 30.3% (95% CI: 5.5, 48.8), and 41.4% (95% CI: 29.0, 51.7)	N/A
Pepin et al. 2019 (138)	Multinational RCT during the 2014/2015 and 2015/2016 influenza seasons	QIIV	Placebo or TIIV (split virion)	Children 6–35 months of age (N=5805)	Laboratory-confirmed influenza caused by any influenza A or B types or by vaccine-similar strains	VE was 51.0% (97% CI: 37.4, 61.9) against influenza caused by A or B type, and 68.4% (47.1, 81.9) against influenza caused by vaccine-like strains	N/A
Esposito et al. 2022 (136)	RCT during three influenza seasons (2017–2019)	QIIV	Non-influenza virus vaccine	Influenza-naïve children 6–35 months of age (N=2000 vaccinated)	Symptomatic influenza virus infection	aVE against any circulating influenza strain was 54% (95% CI: 37, 66)	N/A

Sullender et al. 2019 (145)	Cluster RCT	TIIV	IPV	Children 6 months to 10 years of age (N=4345)	Laboratory-confirmed influenza	Total VE was 25.6% (95% CI: 6.8, 40.6) in year 1 to 74.2% (95% CI: 57.8, 84.3) in year 3.	N/A
Mallory et al. 2020 (141)	Systematic review and meta-analysis of five studies during the 2016/2017 influenza season	IIV	Not specified	Children 6 months to 17 years of age	Laboratory (PCR-, culture- or antigen)-confirmed) influenza	Consolidated VE of 47% (95% CI: 29, 61) against all influenza strains	N/A
Wall et al. 2021 (134)	Analysis of 10 observational VE studies from a systematic review of VE or immunogenicity studies published up to Apr 2019	TIIV or QIIV	No vaccination	Children 6 months to 8 years of age	Hospitalisations, acute respiratory infection, medically attended influenza illness, influenza-like illness, or pneumonia and influenza	N/A	VE for all age groups were higher for fully vaccinated groups (range between 7% [95% CI: −80, 50] and 86% [95% CI: 29, 97]) than partially vaccinated groups (range between −41% [95% CI: −150, 20] and 73% [95% CI: 3, 93])
Diallo et al. 2019 (144)	Cluster RCT in Senegal during the 2008/2009 influenza season	TIIV	IPV	Children 6 months to 10 years of age (N=11,670 eligible)	Laboratory (rRT-PCR)-confirmed symptomatic influenza	N/A	Total and indirect VE against seasonal A/H3N2 influenza were 43.6% (95% CI: 18.6, 60.9) and 15.4% (95% CI: −22.0, 41.3), respectively

Niang et al. 2021 (143)	Consecutive cluster RCTs in 2010 and 2011	TIIV	IPV	Children 6 months to 10 years of age	Laboratory-confirmed influenza	N/A	Total VE against all strains was 52.8% (95% CI: 32.3, 67.0) for year 2
Boddington et al. 2021 (140)	Meta-analysis of 37 studies (test-negative design) published up to Jun 2020	TIIV or QIIV	Not specified	Children 6 months to 17 years of age	Laboratory-confirmed influenza-associated hospitalisation	N/A	VE for all IIVs was 67.1% (95% CI: 53.5, 76.8); 47.5% (95% CI: 39.5, 54.4) for TIIV and 50.2% (95% CI: 10.7, 72.3) for QIIV
Jefferson et al. 2018 (165)	Cochrane review of 41 RCTs published up to Jul 2017	IIV	Placebo or no vaccination	Children 2–16 years of age	Laboratory-confirmed (viral isolation, serological supporting evidence, or both) influenza and ILI	VE for laboratory-confirmed influenza was 64% (95% CI: 52, 72) VE for ILI was 28% (95% CI: 21, 35)	N/A
Adults							
Demicheli et al. 2018 (164)	Cochrane review of 25 RCTs or quasi-RCTs published up to Jul 2017	IIV	Placebo or no vaccination	Adults 16 to 65 years of age	Laboratory-confirmed influenza (viral isolation, serological supporting evidence, or both) and ILI	VE for laboratory-confirmed influenza was 59% (95% CI: 53, 64) VE for ILI was 16% (95% CI: 5, 25)	N/A

Adults ≥65 years of age							
Demicheli et al. 2018 (166)	Cochrane review of eight RCTs published up to Jul 2017	TIIV	Placebo or no vaccination	Adults ≥65 years of age (N=>5000)	Laboratory-confirmed (viral isolation, serological supporting evidence, or both) influenza and ILI	Over a single season: VE for laboratory-confirmed influenza was 58% (95% CI: 34, 73) VE for ILI was 41% (95% CI: 27, 53)	N/A
Pregnant individuals							
Omer et al. 2020 (142)	Pooled analysis of three RCTs		Placebo or meningococcal conjugate vaccine	Pregnant individuals (N=10,002)	Laboratory (PCR)-confirmed influenza	Pooled VE was 50% (95% CI: 32, 63), from enrolment to follow-up at 6 months postpartum	N/A

*Primary outcome data only reported.

†Publications of the same clinical trial (NCT01439360) reporting different outcomes.

aVE, absolute vaccine effectiveness; CI, confidence interval; IIV, inactivated influenza virus vaccine; ILI, influenza-like illness; IPV, inactivated poliovirus vaccine; PCR, polymerase chain reaction; QIIV, quadrivalent inactivated influenza virus vaccine; RCT, randomised controlled trial; RT-PCR, reverse transcription polymerase chain reaction; SD-IIV, standard-dose inactivated influenza virus vaccines; TIIV, trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness.

TABLE 3 Overview of studies included in the review – high-dose inactivated influenza virus vaccines.

Citation / reference	Evidence type / study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)*	Key effectiveness result(s)*
Adults ≥18 years of age							
Comber et al. 2022 (168)	Systematic review and meta-analysis of studies including adults ≥18 years (n=36)	HD-TIIV	SD-TIIV or no vaccination	Adults ≥65 years of age	Laboratory-confirmed influenza	VE was 24% (95% CI: 10, 37) vs SD-TIIV (n=1 RCT)	VE was 89% (95% CI: 47, 100) against influenza B and 22% (95% CI: −82, 66) for influenza A (H3N2) vs no vaccination (n=1 test-negative case control study)
Veroniki et al. 2024 (169)	Systematic review and meta-analysis of studies including adults ≥60 years (n=41)	HD-TIIV	Placebo or SD-TIIV	Adults ≥60 years of age	Laboratory-confirmed influenza/probable ILI	VE was 72.9% (95% CI: 43.5, 86.6) for laboratory-confirmed influenza vs placebo (pairwise and network meta-analysis) VE was 1.8% (95% CI: –1.8, 7.2) for ILI vs SD-TIIV (pairwise meta-analysis)	N/A
Adults ≥65 years of age							
Lee et al. 2018 (151)	Systematic review and meta-analysis of studies	HD-TIIV	SD-TIIV	Adults ≥65 years of age	Laboratory-confirmed influenza/probable ILI	rVE was 19.5% (95% CI: 8.6, 29.0)	N/A

	including adults ≥65 years (n=7)						
Lee et al. 2021 (132)	Updated systematic review and meta-analysis of RCTs and observational studies (n=15) (2009–2019)	HD-TIIV	SD-TIIV/SD-QIIV	Adults ≥65 years of age	Laboratory-confirmed influenza/probable ILI	Pooled rVE was 15.9% (95% CI: 4.1, 26.3) (n=2 RCTs and n=3 observational studies)	Pooled rVE was 15.9% (95% CI: 4.1, 26.3) (n=2 RCTs and n=3 observational studies)
Lee et al. 2023 (150)	Updated systematic review and meta-analysis of RCTs and observational studies (n=21) (2009–2022)	HD-TIIV	SD-TIIV	Adults ≥65 years of age (N=>45 million)	Laboratory-confirmed influenza/probable ILI	Pooled rVE was 24.1% (95% CI: 10.0, 36.1; p=0.002) (n=3 RCTs)	Pooled rVE was 11.1% (95% CI: −0.1, 21.0; p=0.051) (n=8 observational studies)
Skaarup et al. 2024 (170)	Meta-analysis of RCTs including adults ≥65 years (n=5)	HD-TIIV/HD-QIIV	SD-TIIV/SD-QIIV	Adults ≥65 years of age (N=105,685)	Pneumonia and influenza hospitalisation	Pooled rVE was 23.5% (95% CI: 12.3, 33.2) for pneumonia and influenza hospitalisations vs SD-TIIV/SD-QIIV	N/A
Older adults and immune-suppressed adults							
Weissman et al. 2021 (152)	Systematic review and meta-analysis of RCTs (n=16; 47,857 patients)	HD-TIIV	SD-TIIV	Older adults (n=10 trials) and immune-suppressed patients (n=3 trials)	Laboratory-confirmed influenza	Pooled VE was 24% (95% CI: 10, 36)[†]	N/A

*Primary outcome data only reported.

†Outcome stemmed mainly from one trial in older adults.

CI, confidence interval; HD, high dose; ILI, influenza-like illness; RCT, randomised controlled trial; RR, relative risk; rVE, relative vaccine efficacy/effectiveness; SD, standard dose; TIIV, trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness.

TABLE 4 Overview of studies included in the review – adjuvanted inactivated influenza virus vaccines.

Citation / reference	Evidence type / study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)*	Key effectiveness result(s)*
Children ≥6 months of age							
Vesikari et al. 2018 (153)	Multicentre RCT in children over 2 influenza seasons, from 2013–2015	MF59-adjuvanted vaccine (aQIIV)	IIV (TIIV or QIIV)	Children 6 months to 5 years of age (N=10,612)	Laboratory (RT-PCR)-confirmed influenza	rVE was –0.67% (95% CI: –19.81, 15.41) in the overall population rVE was 31.37% (95% CI: 3.14, 51.38) in the 6–23 months subgroup	N/A
Loeb et al. 2021 (154)	Cluster RCT in children from January 2017 to June 2019	MF59-adjuvanted SD vaccine (aTIIV)	IIV (QIIV)	Children 6 months to 6 years of age and family cluster members who did not receive the study vaccine (N=1670)	Laboratory-confirmed (RT-PCR) influenza	rVE against influenza A was 80% (HR: 0.20; 95% CI: 0.06, 0.66) in the vaccinated children	N/A
Adults ≥18 years of age							
Murchu et al. 2023 (167)	Systematic review and meta-analysis of RCTs and RWE studies (n=48)	MF59-adjuvanted vaccine (aTIIV/aQIIV)	IIV (TIIV or QIIV), or no vaccination	Adults ≥18 years of age	Laboratory-confirmed influenza	N/A	VE was 45% (95% CI: 23, 61) for aTIIV vs no vaccination in adults ≥65 years of age

							VE was 51% (95% CI: 54, 84) for aTIIV vs no vaccination in adults ≥18 years of age In terms rVE, there was no significant difference with aTIIV vs TIIV or QIIV in adults or older adults in five studies
Adults ≥65 years of age							
Coleman et al. 2021 (157)	Systematic review and meta-analysis of RWE from non-interventional studies and cluster RCTs conducted during the 2006/07–2019/20 influenza seasons (n=16).	MF59-adjuvanted vaccine (aTIIV/aQIIV)	No vaccination, or SD IIV (TIIV/QIIV), or HD-TIIV	Adults ≥65 years of age	Outpatient and hospital visits due to laboratory-confirmed influenza	aVE was 40.7% (95% CI: 21.9, 54.9) and 58.5% (95% CI: 40.7, 70.9) for aTIIV (vs no vaccination) in preventing outpatient visits and hospital visits, respectively rVE was 13.9% (95% CI: 4.2, 23.5) (vs TIIV), 13.7% (95% CI: 3.1, 24.2) (vs QIIV), and 2.8% (95% CI:	N/A

						−2.9, 8.5) (vs HD-TIIV) for aTIIV in preventing influenza-related medical encounters.	
Domnich and de Waure. 2022 (155)	Systematic review of experimental and observational studies (n=10) up to April 2022	MF59-adjuvanted SD vaccine (aTIIV)	HD-TIIV	Adults ≥65 years of age	Laboratory-confirmed influenza	N/A	aTIIV more effective (p<0.05) vs HD-TIIV against all influenza-related medical encounters (hospitalisations, emergency room, and outpatient visits) for influenza (9.7%; 95% CI: 5.0, 14.2) aTIIV was less effective (p<0.05) vs HD-TIIV against hospitalisations for any respiratory condition (and hospital encounters for coronary artery events (–1.2%; 95% CI: –2.2, –0.2)

Gärtner et al. 2022 (156)	Systematic review of RWE over the 2006/07–2008/09 and 2011/12–2019/20 influenza seasons (n=11 analyses from 9 studies)	MF59-adjuvanted SD vaccine (aTIIV)	TIIV, QIIV and/or HD-TIIV	Adults ≥65 years of age	Influenza-related outcomes	N/A	rVE ranged from 7.5% to 25.6% for aTIIV vs TIIV and 7.1% to 36.3% for aTIIV vs QIIV) rVE was 7.7% [95% CI: 2.3, 12.8] for aTIIV vs HD-TIIV in the 2017/18 season and 6.9% [95% CI: 3.1, 10.6] in the 2018/19 season

*Primary outcome data only reported.

aQIIV, adjuvanted quadrivalent inactivated influenza virus vaccine; aTIIV, adjuvanted trivalent inactivated influenza virus vaccine; aVE, absolute vaccine effectiveness; CI, confidence interval; HD, high dose; HR, hazard ratio; IIV, inactivated influenza virus vaccine; QIIV, quadrivalent inactivated influenza virus vaccine; RCT, randomised controlled trial; RT-PCR, reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy/effectiveness; RWE, real-world evidence; SD, standard dose; TIIV, trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness.

TABLE 5 Overview of studies included in the review – live-attenuated influenza virus vaccines.

Citation / reference	Evidence type / study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)*	Key effectiveness result(s)*
Children and infants ≥6 months of age							
Morimoto et al. 2018 (149)	Systematic review and meta-analysis of eight RCTs conducted during 10 influenza seasons	LAIV	Subjects who were vaccinated for one season and not for the previous season (single vaccine group)	Children 6 months to 11 years of age	Medically-attended influenza according to antigenic matching and to whether the subject received the vaccine for two consecutive seasons (multiple vaccine group)	RR (multiple vs single) for children with antigenic match: 0.61 (95% CI: 0.24, 1.57). RR (multiple vs single) for children with antigenic mismatch: 2.03 (95% CI: 1.20, 3.41)	N/A
Boddington et al. 2021 (140)	Systematic review and meta-analysis of 37 test-negative studies published up to Jun 2020	LAIV	Not specified	Children 6 months to 17 years of age	Laboratory-confirmed influenza-associated hospitalisation	N/A	VE of 44.3% (95% CI: 30.1, 55.7)
Children >2 years of age							
Mallory et al. 2018 (148)	Two RCTs in Japan during the 2014–2015 influenza season	LAIV (quadrivalent)	Study 1: uncontrolled single arm	Children 2–6 years of age in study 1 (N=100) and 7–18	Laboratory (PCR)-confirmed influenza	Study 2: VE for vaccine-matched strains was 100% (95% CI: −1875.3, 100); VE for all influenza strains,	N/A

			Study 2: Placebo	years of age in study 2 (N=1301)	caused by vaccine-matched strains	regardless of match to the vaccine, was 27.5% (95% CI: 7.4, 43.0)	
Jefferson et al. 2018 (165)	Cochrane review of 41 RCTs published up to Jul 2017	LAIV	Placebo or no vaccination	Children 3–16 years of age	Laboratory-confirmed influenza (viral isolation, serological supporting evidence, or both) and ILI	VE for laboratory-confirmed influenza of LAIV vs control was 78% (RR: 0.22 [95% CI: 0.11, 0.41]) in children 3 to 16 years of age VE for ILI of LAIV vs control was 31% (95% CI: 20, 40) in children 3 to 16 years of age	
Mallory et al. 2020 (140, 141)	Systematic review and meta-analysis of five studies during the 2016–2017 season	LAIV (quadrivalent)	Not specified	Children 2–17 years of age	Laboratory (PCR-, culture- or antigen)-confirmed influenza	Consolidated VE of 69% (95% CI: 46, 82) against all influenza strains	N/A
Wang et al. 2020 (147)	RCT in China during the 2016–2017 influenza season	LAIV	Placebo	Chinese children 3–17 years of age (N=1999)	Laboratory-confirmed (RT-PCR) influenza	VE of 62.5% (95% CI: 27.6, 80.6) against all influenza strains, and 63.3% (95% CI: 27.5, 81.5) against H3N2	N/A
Krishnan et al. 2021 (146)	RCT in rural India over 2 years (2015–2017)	LAIV	TIIV, placebo, or IPV	Children 2–10 years of age (N=3041)	Laboratory (rRT-PCR)-confirmed influenza	In year 1, VE was 40.0% (95% CI: 25.2, 51.9) for LAIV vs placebo; rVE of LAIV vs TIV was −46.2% (95% CI: −88.9, −13.1)	Not reported

						In year 2, VE was 51.9% (95% CI: 42.0, 60.1) for LAIV vs placebo; rVE of LAIV vs TIV was 4.2% (95% CI: −19.9, 23.5)	
Children <18 years of age, adults and elderly adults ≥61 years of age							
Minozzi et al. 2022 (131)	Systematic review and meta-analysis of 220 RCTs published up to Dec 2020	LAIV (trivalent/ quadrivalent)	SD-TIIV, HD-TIIV, aTIIV, aQIIV, TIVr, QIVr) or placebo (no vaccination, or non-influenza virus vaccine)	Children <18 years of age (N=100,677); adults 18–60 years of age) and elderly adults ≥61 years of age (N=329,127)	Laboratory-confirmed influenza	In children: rVE for trivalent LAIV vs SD-TIIV was 48% (95% CrI: 18, 68) In adults and elderly adults: rVE for trivalent LAIV vs placebo was 44% (95% CI: 26, 59) rVE for trivalent LAIV vs SD-TIIV was −41% (95% CI: −29, −4)	N/A

*Primary outcome data only reported.

AE, adverse event; aQIV, adjuvanted quadrivalent influenza virus vaccine; aVE, absolute vaccine effectiveness; CI, confidence interval; HD, high dose; LAIV, live attenuated influenza virus vaccine; IPV, inactivated polio vaccine; QIVr, recombinant quadrivalent influenza virus vaccine; RCT, randomised controlled trial; RR, relative risk; rRT-PCR, real-time reverse transcription polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy/effectiveness; SAE, serious adverse event; SD, standard dose; TIV, trivalent influenza virus vaccine; TIVr, recombinant trivalent influenza virus vaccine; VE, vaccine efficacy/effectiveness.

TABLE 6 Overview of studies included in the review – cell-based inactivated influenza virus vaccines (IIVcs).

Citation / reference	Evidence type / study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)*	Key effectiveness result(s)*
Individuals ≥6 months of age							
Coleman et al. 2023 (162)	Systematic review and meta-analysis of RWE studies (n=18) over 3 influenza seasons from 2017–2020	QIIVc	No vaccination, TIIVe or QIIVe	Individuals ≥6 months of age	Laboratory-confirmed influenza	N/A	Pooled aVE was 37.6% (95% CI: 19.4, 55.9) for QIIVc vs 26.1% (95% CI: 6.7, 45.4) for TIIVe/QIIVe (n=5 studies) The overall rVE was 8.4% (95% CI: 6.5, 10.2) for QIIVc vs TIIVe/QIIVe (across all studies) In individuals 4–64 years of age, pooled rVE was 16.2% (95% CI: 7.6, 24.8) for 2017–2018, 6.1% (95% CI: 4.9, 7.3) for 2018–2019, and 10.1% (95% CI: 6.3, 14.0) for 2019–2020 In adults ≥65 years of age pooled rVE was 9.9% (95% CI: 6.9, 12.9) for 2017–2018, and –0.8 (95% CI: –3.5, 1.8) for 2018-2019
Children and adolescents 2–17 years of age							

Nolan et al. 2021 (160)	Multicentre RCT across 3 influenza seasons from 2017–2019	QIIVc	Meningococcal ACWY vaccine	Children and adolescents 2–<18 years of age (N=4514)	Laboratory (RT-PCR and viral culture)-confirmed influenza	VE for QIIVc of 54.6% (95% CI: 45.7, 62.1)	N/A
Adults ≥18 years of age							
Puig-Barberà et al. 2022 (163)	Systematic review and meta-analysis of studies (n=12)	IIVcc	IIVe	Adults ≥18 years of age	Laboratory-confirmed influenza	N/A	Adjusted rVE for IIVcc vs IIVe of 11% (95% CI: 8, 14) in 2017–2018 influenza season and 3% (95% CI: –2, 7) in 2018–2019 influenza season
Jordan et al. 2023 (161)	Systematic review of RCTs and non-randomised intervention studies (n=19)	TIIVc/QIIVc	Efficacy: Placebo Effectiveness: no vaccination or IIV	Adults ≥18 years of age	Laboratory-confirmed influenza	VE of 70.1% (95% CI: 60.7, 77.3) vs placebo in adults 18–49 years of age (n=2 RCTs)	In adults ≥18 years, OR of 0.21 (95% CI: −0.12, –0.44) and 0.52 (95% CI: 0.36, 0.64) vs no vaccination (n=2 RCTs) In adults ≥65 years, OR of 0.10 (95% CI: −0.44, 0.44) vs no vaccination and OR of 0.06 (95% CI: −0.46, 0.39) vs IIV

*Primary outcome data only reported.

AE, adverse event; aVE, absolute vaccine effectiveness; CI, confidence interval; IIV, inactivated influenza virus vaccine; IIVcc, seed cell cultured inactivated influenza virus vaccine; IIVe, egg-based inactivated influenza virus vaccine; OR, odds ratio; QIIVc, cell-based quadrivalent inactivated influenza virus vaccine; QIIVe, egg-based quadrivalent inactivated influenza virus vaccine; RCT, randomised controlled trial; RT-PCR, reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy/effectiveness; RWE, real-world evidence; SD, standard dose; TIIVc, cell-based trivalent inactivated influenza virus vaccine; TIIVe, egg-based trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness

TABLE 7 Overview of studies included in the review – recombinant influenza virus vaccines.

Citation / reference	Evidence type / study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)*	Key effectiveness result(s)*
Adults ≥18 years of age							
Evans et al. 2022 (159)	Phase 2b RCT during Apr and Oct 2019	MVA-NP+M1	Placebo (saline)	Non-immuno-suppressed adults ≥18 years of age who received the 2019 QIIV within 28 days of randomisation (N=2152)	Laboratory-confirmed influenza	Incidence of laboratory-confirmed influenza was 3.25% (95% CI: 2.31, 4.44) for MVA-NP+M1 vs 2.14% (95% CI: 1.39, 3.14) for placebo (Fisher's exact, p=0.14)	N/A
Murchu et al. 2023 (158)	Systematic review of RCTs and non-randomised intervention studies (n=10) up to February 2020	TIVr/QIVr	TIIV, QIIV or placebo	Adults ≥18 years of age	Laboratory-confirmed influenza	rVE of 30% (95% CI: 10, 47) for QIVr vs QIIV in adults ≥50 years of age during the 2014–2015 influenza season (n=1 RCT) rVE of 44.6% (95% CI: 18.8, 62.6) for TIVr vs placebo in adults 18–55 years of age during the 2007–2008 influenza season (n=1 RCT)	N/A

Hsiao et al. 2023 (171)	Cluster-randomised observational study including adults 18–64 years of age	QIVr	SD-QIIV	Adults 18–64 years of age (N=1,630,328)	Laboratory-confirmed influenza	N/A	rVE of 15.3% (95% CI: 5.9, 23.8; p = 0.002) versus SD-QIIV in participants aged 50–64 years of age (n=675,252)
Veroniki et al. 2024 (169)	Systematic review and meta-analysis of studies including adults ≥60 years (n=41)	TIVr/QIVr (Combined)	Placebo	Adults ≥60 years of age	Laboratory-confirmed influenza	VE of 70.6% (95% CI: 22.9, 90.2) versus placebo (pairwise and network meta-analysis, n=9 RCTs)	N/A

*Primary outcome data only reported.

CI, confidence interval; IIV, inactivated influenza virus vaccine; ILI, influenza-like illness; MVA-NP+M1, modified vaccinia Ankara expressing virus nucleoprotein and matrix protein 1; QIIV, quadrivalent inactivated influenza virus vaccine; QIVr, recombinant quadrivalent influenza virus vaccine; RCT, randomised controlled trial; RR, relative risk; rVE, relative vaccine efficacy/effectiveness; SAE, serious adverse event; SD, standard dose; TIIV, trivalent inactivated influenza virus vaccine; TIVr, recombinant trivalent influenza virus vaccine.

Figure 1

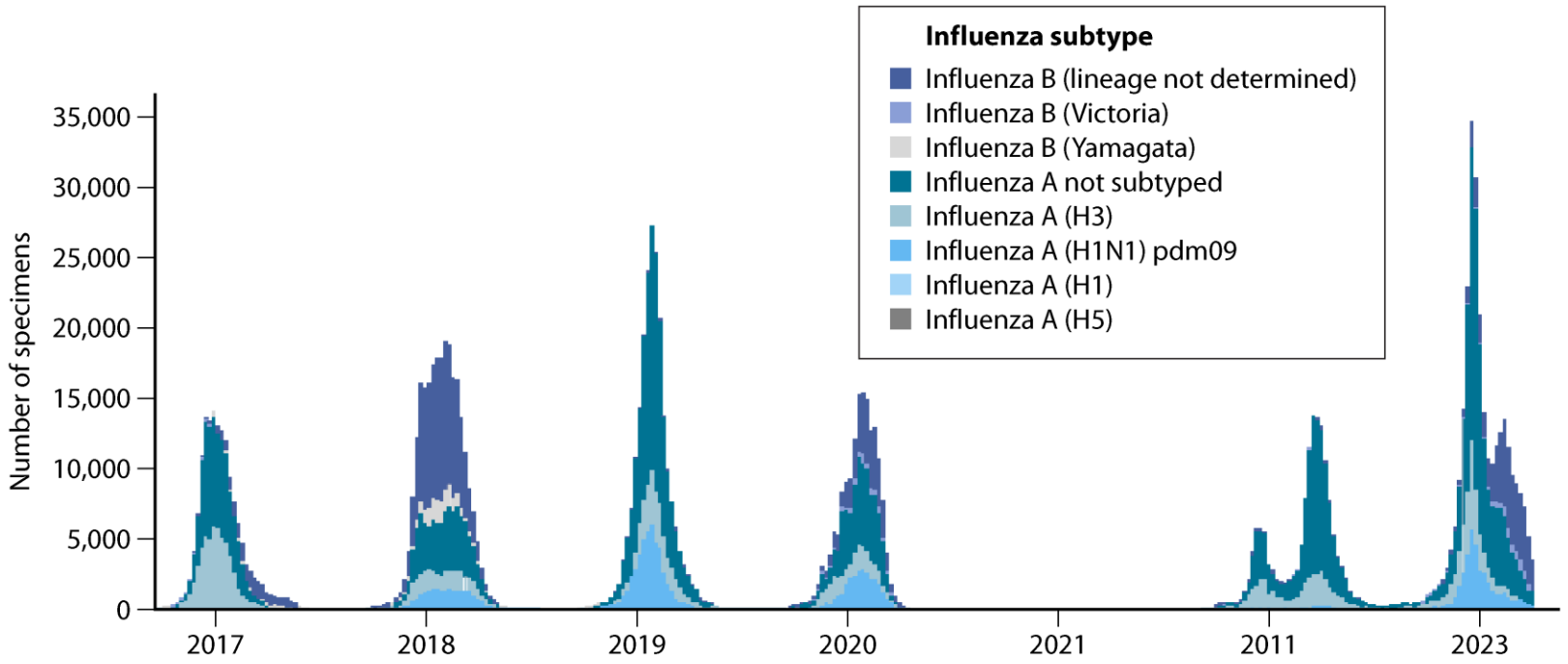

Influenza subtype
Influenza B (lineage not determined)
Influenza B (Victoria)
Influenza B (Yamagata)
Influenza A not subtyped
Influenza A (H3)
Influenza A (H1N1) pdm09
Influenza A (H1)
Influenza A (H5)
Number of specimens
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
2017
2018
2019
2020
2021
2011
2023

Figure 2

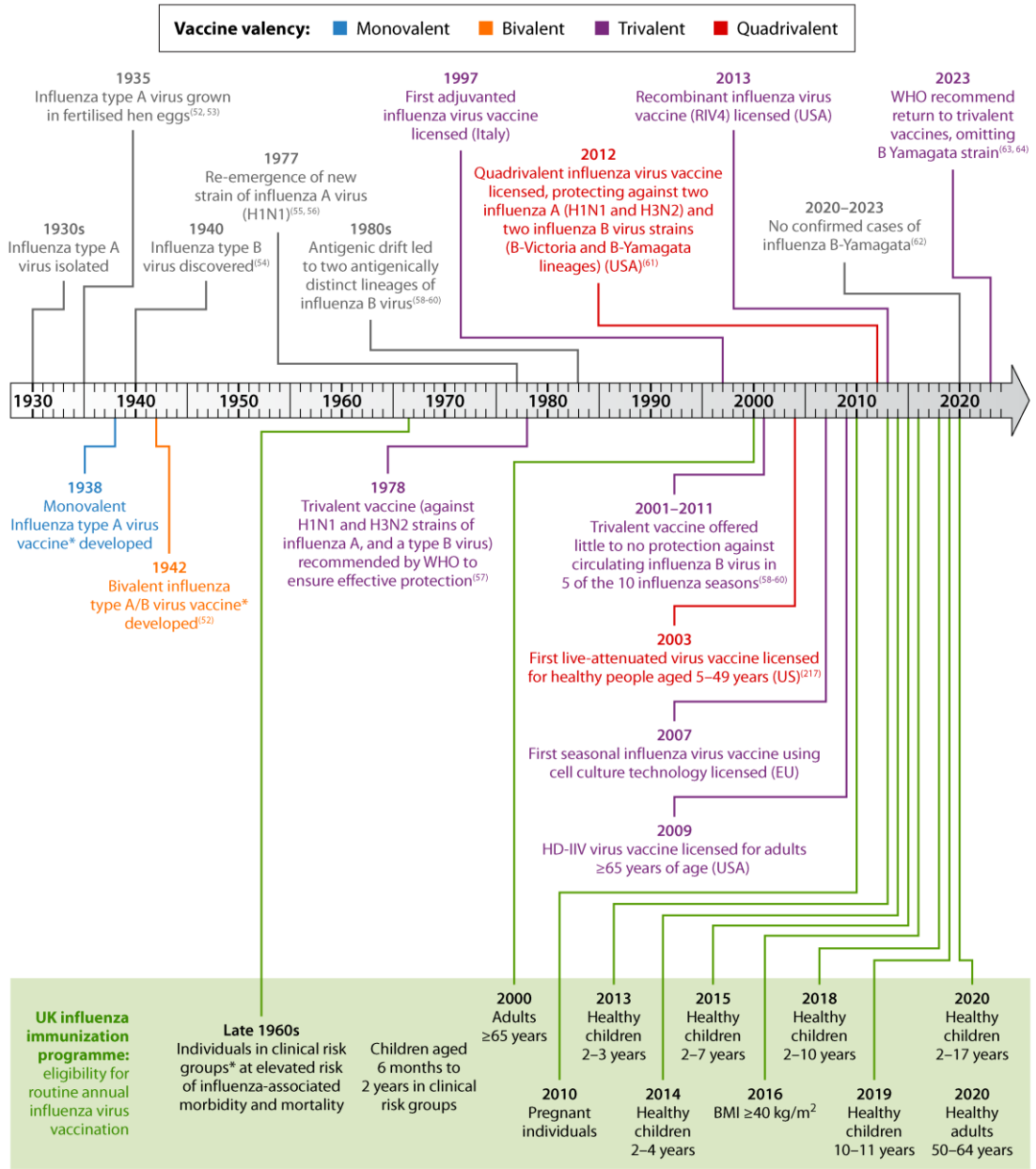
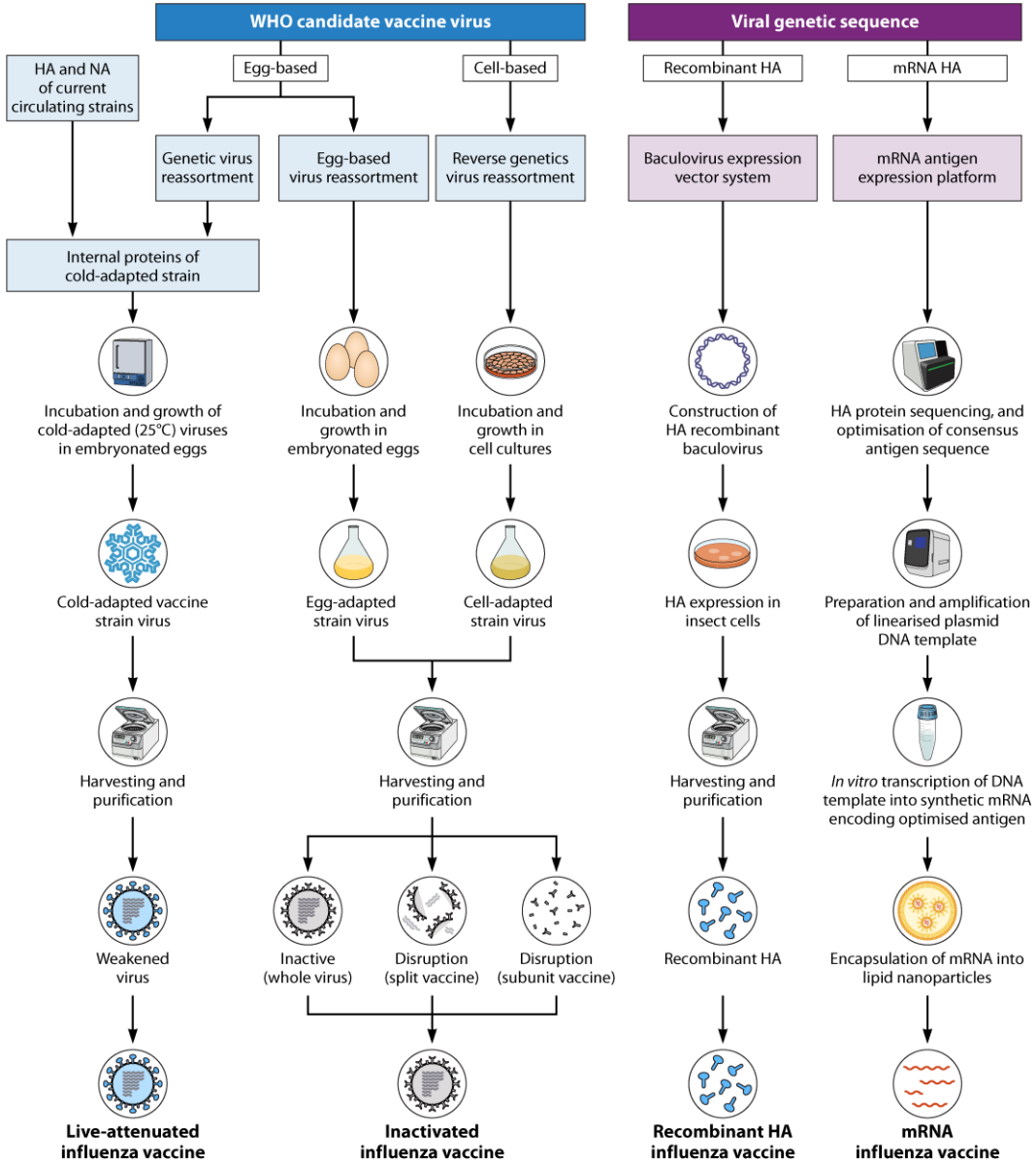

Vaccine valency: Monovalent Bivalent Trivalent Quadrivalent
1935
Influenza type A virus grown in fertilised hen eggs[52, 53]
1997
First adjuvanted influenza virus vaccine licensed (Italy)
2013
Recombinant influenza virus vaccine (RIV4) licensed (USA)
2023
WHO recommend return to trivalent vaccines, omitting B Yamagata strain[63, 64]
1977
Re-emergence of new strain of influenza A virus (H1N1)[55, 56]
2012
Quadrivalent influenza virus vaccine licensed, protecting against two influenza A (H1N1 and H3N2) and two influenza B virus strains (B-Victoria and B-Yamagata lineages) (USA)[61]
1930s
Influenza type A virus isolated
1940
Influenza type B virus discovered[54]
1980s
Antigenic drift led to two antigenically distinct lineages of influenza B virus[58-60]
2020–2023
No confirmed cases of influenza B-Yamagata[62]
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
1938
Monovalent Influenza type A virus vaccine* developed
1942
Bivalent influenza type A/B virus vaccine* developed[52]
1978
Trivalent vaccine (against H1N1 and H3N2 strains of influenza A, and a type B virus) recommended by WHO to ensure effective protection[57]
2001–2011
Trivalent vaccine offered little to no protection against circulating influenza B virus in 5 of the 10 influenza seasons[58-60]
2003
First live-attenuated virus vaccine licensed for healthy people aged 5–49 years (US)[217]
2007
First seasonal influenza virus vaccine using cell culture technology licensed (EU)
2009
HD-IIV virus vaccine licensed for adults ≥65 years of age (USA)
UK influenza immunization programme: eligibility for routine annual influenza virus vaccination
Late 1960s
Individuals in clinical risk groups* at elevated risk of influenza-associated morbidity and mortality
Children aged 6 months to 2 years in clinical risk groups
2000
Adults ≥65 years
2013
Healthy children 2–3 years
2015
Healthy children 2–7 years
2018
Healthy children 2–10 years
2020
Healthy children 2–17 years
2010
Pregnant individuals
2014
Healthy children 2–4 years
2016
BMI ≥40 kg/m2
2019
Healthy children 10–11 years
2020
Healthy adults 50–64 years

Figure 3


WHO candidate vaccine virus
Viral genetic sequence
HA and NA of current circulating strains
Egg-based
Cell-based
Recombinant HA
mRNA HA
Genetic virus reassortment
Egg-based virus reassortment
Reverse genetics virus reassortment
Baculovirus expression vector system
mRNA antigen expression platform
Internal proteins of cold-adapted strain
Incubation and growth of cold-adapted (25°C) viruses in embryonated eggs
Incubation and growth in embryonated eggs
Incubation and growth in cell cultures
Construction of HA recombinant baculovirus
HA protein sequencing, and optimisation of consensus antigen sequence
Cold-adapted vaccine strain virus
Egg-adapted strain virus
Cell-adapted strain virus
HA expression in insect cells
Preparation and amplification of linearised plasmid DNA template
Harvesting and purification
Harvesting and purification
Harvesting and purification
In vitro transcription of DNA template into synthetic mRNA encoding optimised antigen
Weakened virus
Inactive (whole virus)
Disruption (split vaccine)
Disruption (subunit vaccine)
Recombinant HA
Encapsulation of mRNA into lipid nanoparticles
Live-attenuated influenza vaccine
Inactivated influenza vaccine
Recombinant HA influenza vaccine
mRNA influenza vaccine

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Supplemental material

Recent advances in the influenza virus vaccine landscape: a comprehensive overview of technologies and trials

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Methodology

Methodology

We conducted a literature search in the PubMed database and Cochrane Library using the search terms and filters displayed in Table S1. Searches were limited to articles published during a ~six-year period from 01 January 2018 to 15 July 2024, in English language only. The initial date of 2018 was chosen as this is when the enhanced influenza virus vaccines (i.e. those other than standard-dose egg-based influenza virus vaccines) became available in the UK and were recommended more consistently compared with standard-dose egg-based vaccines in other countries. To promote inclusion of high-quality studies filters were applied to include only randomised controlled trials, systematic reviews and meta-analyses. The search returned a total of 261 publications (PubMed) and 17 reviews (Cochrane Library), and an additional four publications that met the inclusion criteria were identified in a separate ‘manual search’ (Fig. S1). The results of the searches were screened and any duplicates removed; titles/abstracts or, if required, full text, were examined to determine suitability for inclusion based on prespecified inclusion/exclusion criteria (Table S2). Articles were excluded if they were pre-clinical, non-clinical, or animal studies, pooled, post hoc, or secondary analyses, included data on immunogenicity and/or safety only, were descriptive/narrative reviews, reported data for vaccines not included in the criteria (or as an intervention as co-administered with another vaccine), reported outcomes other than related to efficacy/effectiveness, were cost-effectiveness studies, or trial registration records, or when the vaccine type was not specified/could not be identified.

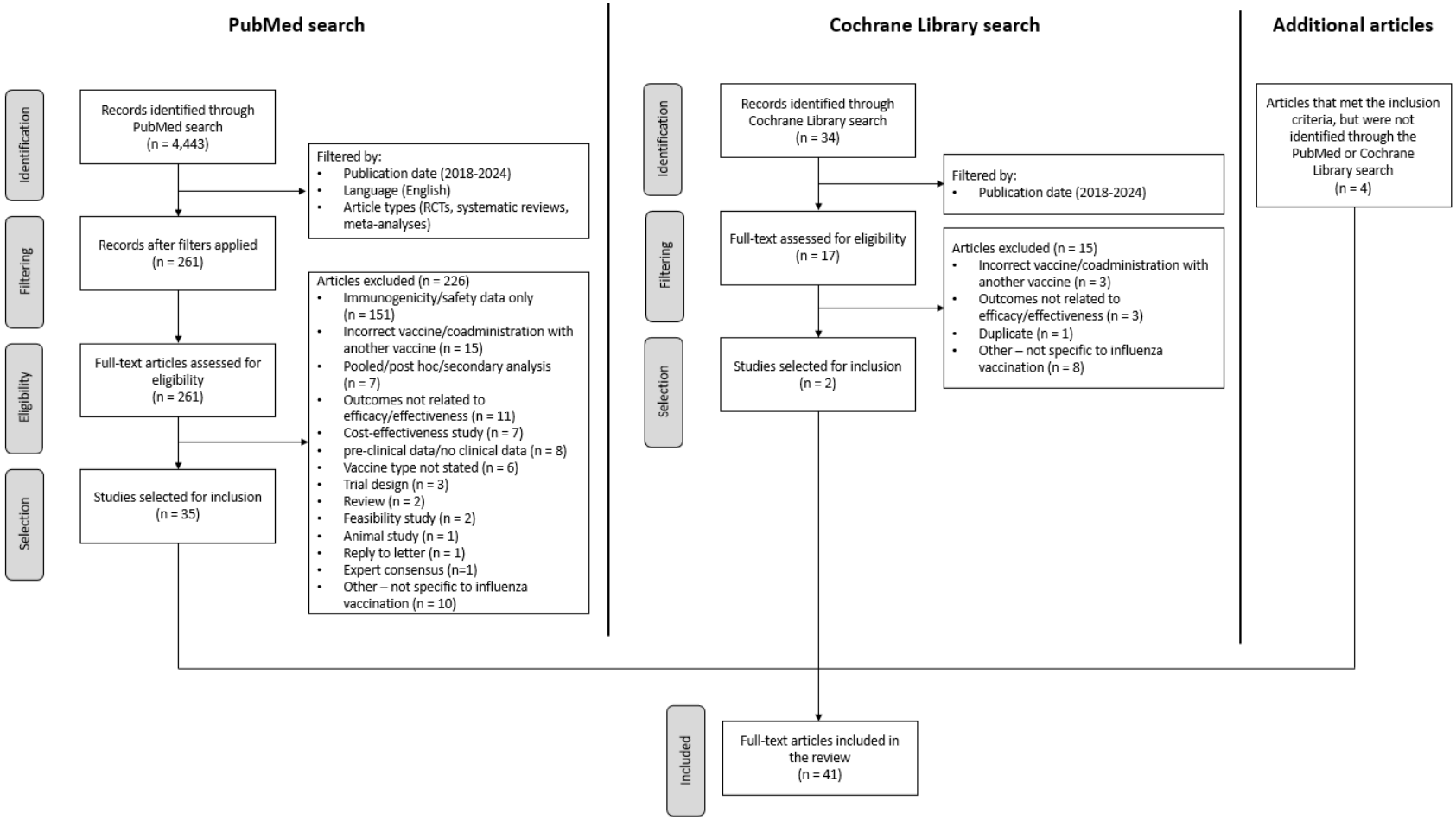
TABLE S1 Search strategy

Search engine	Search terms	Filters
PubMed	(influenza vaccine[Title/Abstract]) AND ((inactivated[Title/Abstract]) OR (egg-based[Title/Abstract]) OR (cell-based[Title/Abstract]) OR (high dose[Title/Abstract]) OR (adjuvant[Title/Abstract]) OR (live-attenuated[Title/Abstract]) OR (LAIV[Title/Abstract]) OR (recombinant[Title/Abstract]) OR (mRNA[Title/Abstract]))	Publication date 01 January 2018 to 15 July 2024 English language only RCT, systematic review, meta-analysis
Cochrane Library	(influenza vaccine) AND (efficacy OR effectiveness)	Publication date 01/01/2018–15/07/2024

TABLE S2 Eligibility criteria for selection of articles

Eligibility	**Criteria**
Inclusion	Studies reporting on vaccine efficacy/effectiveness
Exclusion	Pre-clinical studies
	Animal studies
	Non-clinical studies
	Immunogenicity/safety data only
	Incorrect vaccine (or intervention as co-administration with another vaccine)
	Cost-effectiveness studies
	Vaccine type not specified
	Outcomes other than efficacy/effectiveness
	Pooled analysis
	Post hoc/secondary analysis
	Feasibility studies
	Trial registration
	Reviews
	Other – not specific to influenza vaccination

FIG S1 Articles selection flowchart



RCT, randomised controlled trial