AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Public Health | Review

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

Tristan W. Clark,[1] John S. Tregoning,[2] Helen Lister,[3] Tiziano Poletti,[3] Femy Amin,[3] Jonathan S. Nguyen-Van-Tam[4]

AUTHOR AFFILIATIONS See affiliation list on p. 29.

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 National Health Service (NHS) through increased primary and emergency care visits and subsequent hospitalizations. Population groups ≤4 years and ≥65 years of age, and those with underlying health conditions, are at the greatest risk of influenza-related hospitalization. Recent advances in influenza virus vaccine

Editor Graeme N. Forrest, Rush University Medical Center, Chicago, Illinois, USA

Address correspondence to Helen Lister, helen.lister@sanofi.com.

Tristan W. Clark and John S. Tregoning contributed equally to this article. Author order was determined alphabetically.

T.W.C. has received speaker fees, honoraria, travel reimbursement, and equipment and consumables at discount or free of charge for the purposes independent of research, outside of this submitted study, from BioFire diagnostics, bioMérieux, QIAGEN, SenseBio Detection, and Inflammatix. He has received consultancy fees from BioFire, Cepheid, Synairgen Research, Roche, and Janssen. He has received honoraria for participation in advisory boards from Cepheid, Roche, Janssen, Shionogi, Sanofi, Seqirus, and GSK. He is a member of an independent data monitoring committee for a trial sponsored by Roche. He has acted as the UK chief investigator for a study sponsored by Janssen. He owns shares in Synairgen Research. J.S.N.-V.-T. was seconded to the Department of Health and Social Care, England (DHSC) between October 2017 and March 2022. After this assignment was completed, he reports lecture fees from AstraZeneca, Sanofi, Seqirus, and Gilead; also consulting fees from Roche, Seqirus, Janssen, Sanofi, and Moderna. The views expressed in this manuscript are those of its authors and not necessarily those of DHSC, its Agencies, or any of the above entities. J.S.T. has advised the Sanofi influenza vaccine program and received consultancy fees from Touchlight Genetics. H.L., T.P., and F.A. are employees of Sanofi and may hold stocks or shares and accrued pension rights in the company.

See the funding table on p. 29.

Published 3 October 2024

technologies may help to mitigate this burden. This review aims to summarize 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.

KEYWORDS adjuvanted, inactivated, influenza virus, LAIV, live attenuated, prevention, recombinant, vaccine efficacy, vaccine safety, vaccine technologies

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 hospitalizations 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 is now comparable with levels recorded before the pandemic (Fig. 1) (7, 8). In England during the 2022/23 influenza season, there were 8,751 hospitalized 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 hospitalization (10). Other population subgroups at risk of severe influenza disease or complications include those with chronic medical or immunosuppressive conditions,

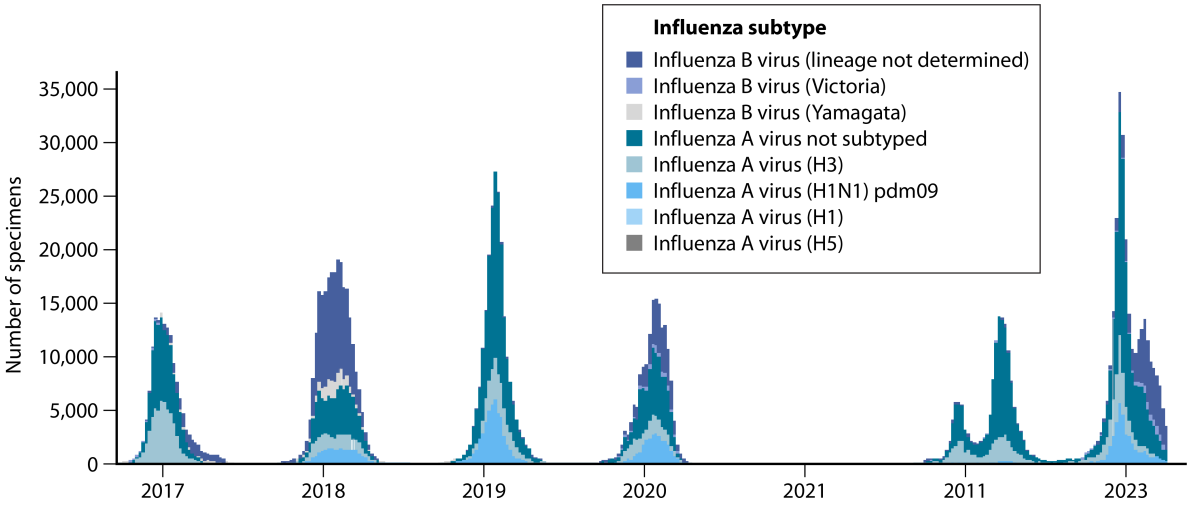

FIG 1 Influenza virus samples analyzed by GISRS for the WHO European Region from the 2016/2017 to the 2022/2023 influenza seasons (7). Data are from FluNet (https://www.who.int/tools/flunet) (7). Changes have been made to the style and format of the figure in accordance with the license (https://creativecommons.org/compatiblelicenses). GISRS, Global Influenza Surveillance and Response System; WHO, World Health Organization.

TABLE 1 Risk groups who should be offered influenza virus vaccination according to UK government guidelines (11)[a,b]

Clinical risk category	Examples (this list is not exhaustive, and decisions should be based on clinical judgment)
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 including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, and bronchopulmonary dysplasia. 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 ischemic heart disease. This includes individuals with atrial fibrillation, peripheral vascular disease, or a history of venous thromboembolism.
Chronic kidney disease	Chronic kidney disease at stages 3, 4, or 5, chronic kidney failure, nephrotic syndrome, and kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, and chronic hepatitis.
Chronic neurological disease	Stroke, transient ischemic attack. Conditions in which respiratory function may be compromised due to neurological or neuromuscular disease (for example, polio syndrome sufferers). Clinicians should offer immunization, based on individual assessment, to clinically vulnerable individuals including those with cerebral palsy, severe or profound, and multiple learning disabilities, 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 hypoglycemic drugs, and 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, and severe combined immunodeficiency (SCID)]. Individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-tumor necrosis factor (TNF) alemtuzumab, ofatumumab, and rituximab, and patients receiving protein kinase inhibitors or poly (ADP-ribose) polymerase (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 hematological malignancy, including leukemia, 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, thalassemia major, and celiac syndrome that may lead to splenic dysfunction.
Morbid obesity (class III obesity)[b]	Adults with a body mass index ≥40 kg/m^2.

[a]Adapted from Green book chapter 19 (11) under the version 3.0 of the Open Government Licence.
[b]Many of this patient group will already be eligible due to complications of obesity that place them in another risk category.

such as 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 hospitalization in pregnant women and can cause harm to the developing fetus (16, 17). Inactivated influenza virus (IIV) 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 hospitalization 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 hemagglutinin (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 recognized 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 viruses 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 that are novel in humans, they can result in a new influenza A virus 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 the 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 fertilized 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 5 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

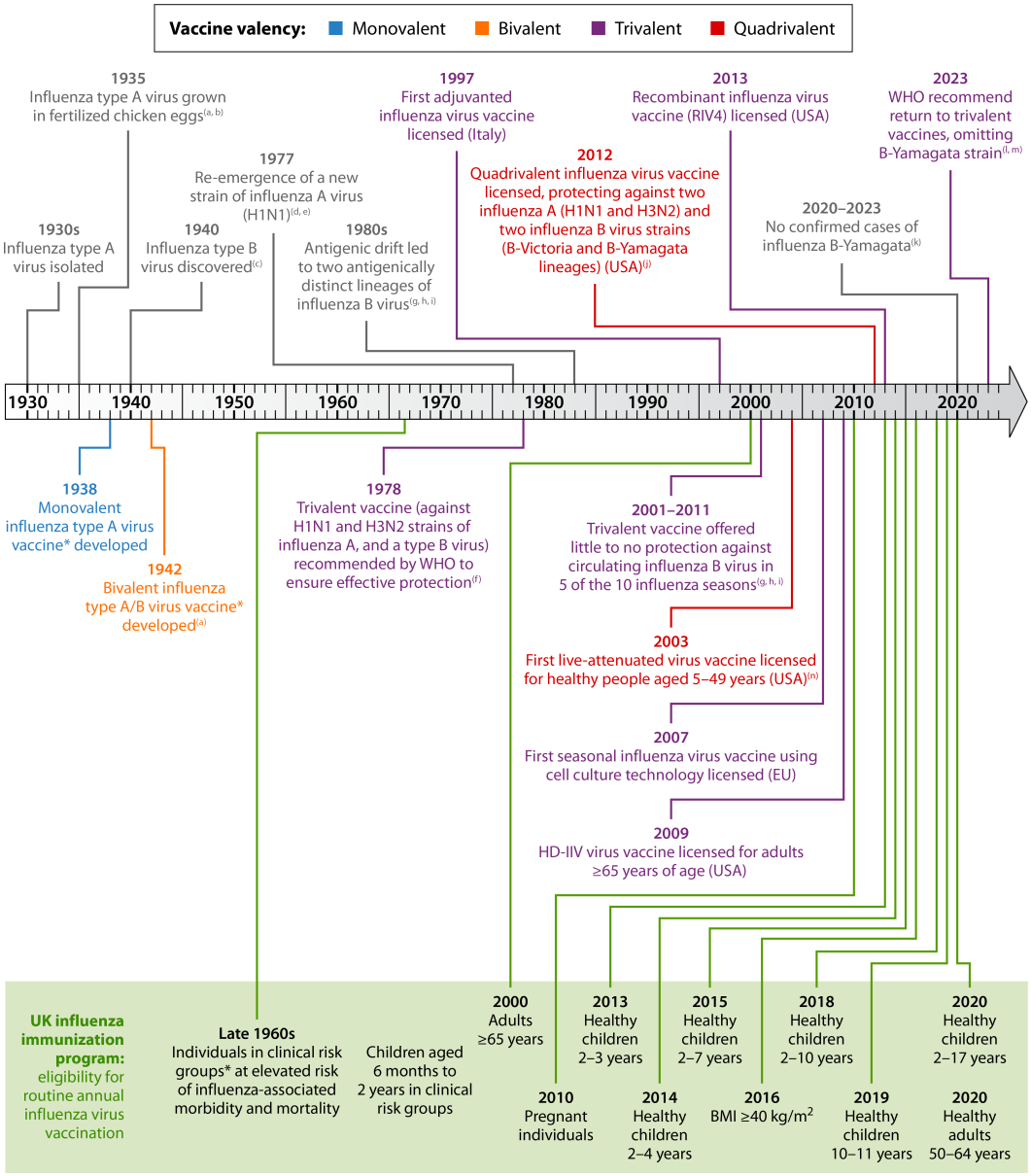

FIG 2 History of the development of influenza virus vaccines and development of the UK immunization program. Eligibility was introduced for healthy adults in 2020 in the UK but was removed in 2023 in England, Wales, and Northern Ireland (they remain in Scotland at time of publication). Superscript letters in the figure represent references as follows. (a) See reference (52). (b) See reference (53). (c) See reference (54). (d) See reference (55). (e) See reference (56). (f) See reference (57). (g) See reference (58). (h) See reference (59). (i) See reference (60). (j) See reference (61). (k) See reference (62). (l) See reference (63). (m) See reference (64). (n) See reference (65). *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 (11). BMI, body mass index; EU, European Union; US, United States.

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 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 necessitate 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 centers around the world send isolated viruses for genetic and antigenic characterization to WHO collaborating centers, including the Francis Crick WHO collaborating center in the UK (66), and data from these centers are used to inform the recommendations on the composition of the influenza virus vaccine required for protection in the next season (64, 67, 68).

In the UK, national surveillance is conducted by the UK Health Security Agency, 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 (69–71), which can inform local recommendations (72).

National immunization programs

Most national influenza policies recommend vaccinating specific populations at increased risk of influenza-related complications (15, 73, 74). Recommendations across National Immunization 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 (72, 75–77). 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 (78).

To ensure that NITAG policy recommendations are consistent and transparent, the WHO recommends the use of a systematic, standardized decision-making process (79). The quality of evidence should be assessed using methods such as Grading of Recommendations Assessment, Development, and Evaluation (80), 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, 77). 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) (77, 81–85).

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 (86). Several countries have advance purchase agreements for pandemic-specific influenza virus vaccines, including the UK, USA, and Australia (87–89). The mRNA platform will be a key part of the pandemic vaccine response due to its ability to facilitate the rapid incorporation of new antigens, as demonstrated during the COVID-19 pandemic (90, 91). 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 (86, 92). The increased genetic exchange among influenza viruses in wild aquatic birds, commercial and domestic poultry, pigs, and humans poses a continuing threat to humanity (86). 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 (93–96). There have been cases of interspecies transmission to humans (94, 97–99), and the situation is being continuously monitored by health authorities worldwide (100–103). 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 (104).

Influenza virus vaccine technologies

From the 1940s to the 2010s, 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 (105). 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] (106–112). Although these technologies have been previously described to varying extents (105, 113–117), there is no recently 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.

MATERIALS AND METHODS

Literature searches

We conducted a literature search in the PubMed database and Cochrane Library covering a ~6-year period from 01 January 2018 to 15 July 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 randomized 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-PCR, or a rapid influenza diagnostic test), influenza-like illness (ILI), or influenza-related hospitalization. There is no standard, international definition of ILI; the majority of studies in this review defined ILI as a clinical diagnosis based on symptoms, such as headache, high temperature, cough, and muscle pain. The WHO defines ILI as an acute respiratory infection with onset within the past 10 days, presenting with cough and a measured temperature of ≥38°C (118), and the Centers for Disease Control and Prevention (CDC) as fever ≥37.8°C and cough and/or sore throat (119).

Although immunogenicity data are a main criterion for annual re-licensure, they are not described here due to the lack of global standardization for measuring protective immune response using methods such as hemagglutination-inhibition assays (120) and uncertainties related to correlation with clinical protection (121, 122). Some studies have examined the impact of influenza virus vaccines on conditions more broadly associated with influenza, e.g., cardiovascular disease (29, 123–130), 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 (Tables 2 to 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 summarized. 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 randomization 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 titers 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 titers 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 focused 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

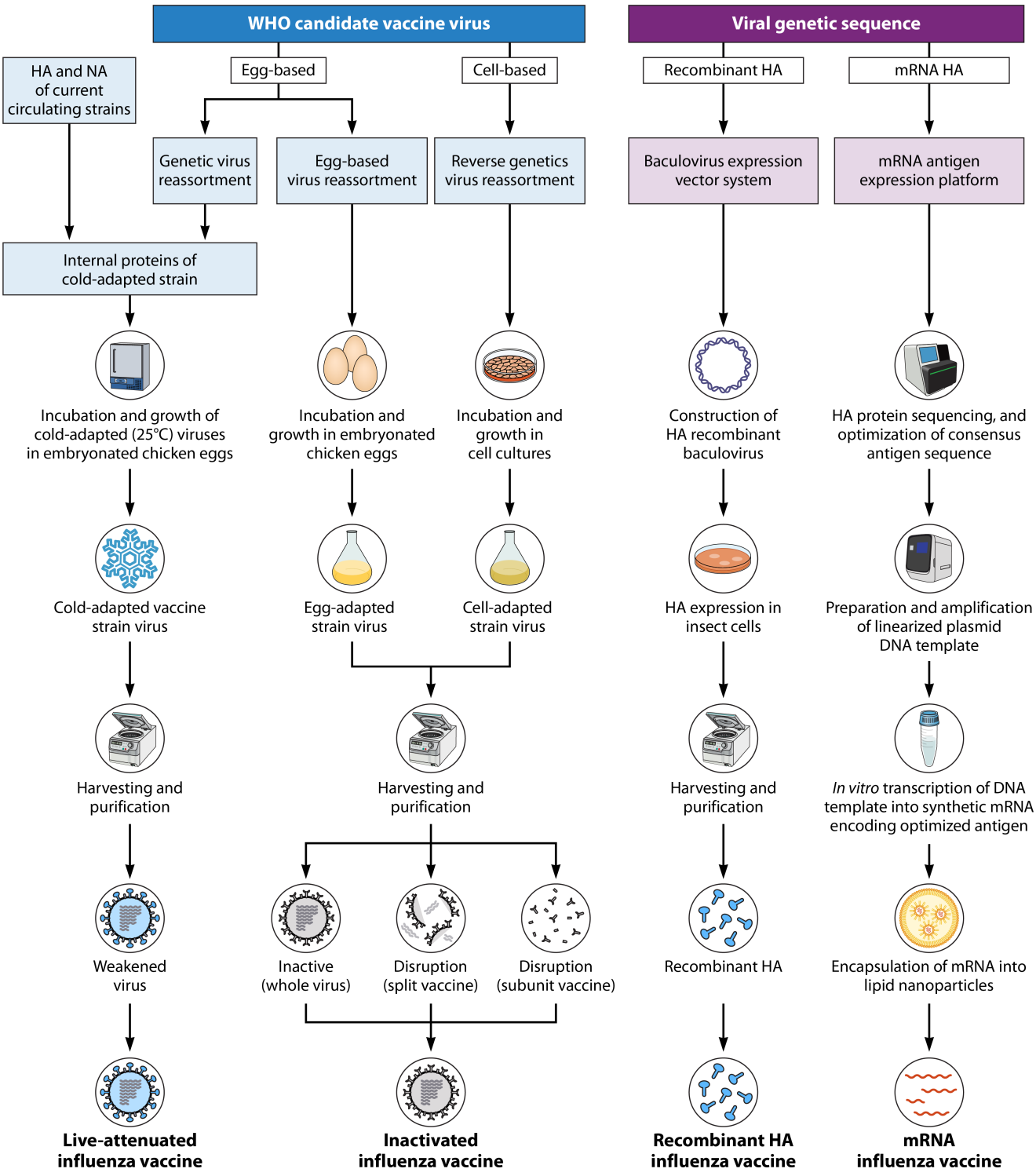

FIG 3 Overview of egg-based, cell-based, recombinant, and mRNA vaccine technologies. DNA, deoxyribonucleic acid; HA, hemagglutinin; mRNA, messenger ribonucleic acid.

that its impact will likely be limited to influenza seasons in which H3N2 strains dominate (77). 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 immunization programs.

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

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 through physical manipulation by 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 the 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) (116). The current standard dose of TIIV and QIIV formulations contain, in addition to the other viral components, a standardized 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 to 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 the 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 the 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).

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)[a]	Key effectiveness result(s)[a]
Infants ≤6 months of age							
Jarvis et al. (133)	Meta-analysis of two RCTs from a systematic review of RCTs and observational studies published up to October 2019	IIV	Placebo (saline)	Infants ≤6 months of age following maternal influenza virus vaccination (*N* = 5,742)	Laboratory (PCR)-confirmed influenza	Pooled VE of 34% (95% CI: 15, 50)	N/A
Children and infants ≥6 months of age							
Claeys et al. (139)[b]	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[c]
Danier et al. (137)[b]	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 was 46% less frequent [crude odds ratio 0.54 (95% CI: 0.39, 0.75)]	N/A
Dbaibo et al. (135)[b]	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. (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* = 5,805)	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. (136)	RCT during three influenza seasons (2017–2019)	QIIV	Non-influenza virus vaccine	Influenza-naïve children 6–35 months of age (*N* = 2,000 vaccinated)	Symptomatic influenza virus infection	aVE against any circulating influenza strain was 54% (95% CI: 37, 66)	N/A
Sullender et al. (145)	Cluster RCT	TIIV	IPV	Children 6 months to 10 years of age (*N* = 4,345)	Laboratory-confirmed influenza	Total VE was 25.6% (95% CI: 6.8, 40.6) in 1 year to 74.2% (95% CI: 57.8, 84.3) in 3 year.	N/A
Mallory et al. (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. (134)	Analysis of 10 observational VE studies from a systematic review	TIIV or QIIV	No vaccination	Children 6 months to 8 years of age	Hospitalizations, acute respiratory	N/A	VE for all age groups were higher for fully vaccinated groups (range

(*Continued on next page*)

TABLE 2 Overview of studies included in the review—standard-dose inactivated influenza virus vaccines (*Continued*)

Citation/reference	Evidence type/study design	Vaccine investigated	Control/comparator	Study population	Primary study outcome	Key efficacy result(s)[a]	Key effectiveness result(s)[a]
	of VE or immunogenicity studies published up to April 2019				infection, medically attended influenza illness, influenza-like illness, or pneumonia and influenza		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. (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. (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. (140)	Meta-analysis of 37 studies (test-negative design) published up to June 2020	TIIV or QIIV	Not specified	Children 6 months to 17 years of age	Laboratory-confirmed influenza-associated hospitalization	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. (165)	Cochrane review of 41 RCTs published up to July 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. (164)	Cochrane review of 25 RCTs or quasi-RCTs published up to July 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. (166)	Cochrane review of eight RCTs published up to July 2017	TIIV	Placebo or no vaccination	Adults ≥65 years of age (*N* ≥ 5,000)	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							

(*Continued on next page*)

TABLE 2 Overview of studies included in the review—standard-dose inactivated influenza virus vaccines (*Continued*)

Citation/reference	Evidence type/study design	Vaccine investigated	Control/comparator	Study population	Primary study outcome	Key efficacy result(s)[a]	Key effectiveness result(s)[a]
Omer et al. (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

[a]Primary outcome data only reported.
[b]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; QIIV, quadrivalent inactivated influenza virus vaccine; RCT, randomized controlled trial; RT-PCR, reverse transcription PCR; SD-IIV, standard-dose inactivated influenza virus vaccines; TIIV, trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness.
[c]N/A, not applicable.

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 utilized, particularly in younger cohorts, and are used in national immunization programs (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 (77).

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 titers 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, the use of high-dose TIIV/QIIV was associated with reduced risk of hospitalization 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 signaling pathways, leading to enhanced chemokine and cytokine secretion and activation of immune cells (197, 198). Common vaccine adjuvants include

TABLE 3 Overview of studies included in the review—high-dose inactivated influenza virus vaccines[a]

Citation/reference	Evidence type/study design	Vaccine investigated	Control/comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
Adults ≥18 years of age							
Comber et al. (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. (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. (151)	Systematic review and meta-analysis of studies including adults ≥65 years (*n* = 7)	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
Lee et al. (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. (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. (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 hospitalization	Pooled rVE was 23.5% (95% CI: 12.3, 33.2) for pneumonia and influenza hospitalizations vs SD-TIIV/SD-QIIV	N/A
Older adults and immune-suppressed adults							
Weissman et al. (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)[c]	N/A[d]

[a]CI, confidence interval; HD, high dose; ILI, influenza-like illness; RCT, randomized controlled trial; RR, relative risk; rVE, relative vaccine efficacy/effectiveness; SD, standard dose; TIIV, trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness.
[b]Primary outcome data only reported.
[c]Outcome stemmed mainly from one trial in older adults.
[d]N/A, not applicable.

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 potentially improved immunogenicity of adjuvanted vs 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 multicenter RCT in children 6 months to 5 years of age, over two influenza seasons (2013–2015), showed an 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-randomized 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 vs non-adjuvanted TIIVs, and from 7.1% to 36.3% vs 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, and 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, 105, 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 the 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 or licensed for use in those >18 years age in the UK (77). However, LAIVs are licensed in the USA in adults ≤49 years of age (65). Due to the potential risk of infection from using live viruses for immunization, 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 reduces vaccine effectiveness (Fig. 3) (109, 217–219). 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, 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 (220, 221). The virus-containing fluid is then collected and the virus antigen is purified (220, 221).

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 is unaffected by potential egg shortages (105). Furthermore, cell-based technologies largely overcome the issues of egg adaptation seen with egg-based influenza manufacturing (222–224). However, cell-based mutations in the HA and NA proteins occur less frequently than mutations in egg-based

TABLE 4 Overview of studies included in the review—adjuvanted inactivated influenza virus vaccines[a]

Citation/reference	Evidence type/study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
Children ≥6 months of age							
Vesikari et al. (153)	Multicenter RCT in children over two 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[c]
Loeb et al. (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* = 1,670)	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. (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. (157)	Systematic review and meta-analysis of RWE from non-interventional studies and cluster RCTs conducted during the 2006/2007–2019/2020 influenza seasons (*n* = 16).	MF59-adjuvanted vaccine (aTIIV/aQIIV)	No vaccination, 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: –2.9, 8.5; vs HD-TIIV) for aTIIV in preventing influenza-related medical encounters.	N/A
Domnich and de Waure (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 (hospitalizations, 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 hospitalizations for any respiratory condition (and hospital encounters for

(*Continued on next page*)

TABLE 4 Overview of studies included in the review—adjuvanted inactivated influenza virus vaccines[a] (*Continued*)

Citation/reference	Evidence type/study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
							coronary artery events (–1.2%; 95% CI: –2.2,–0.2)
Gärtner et al. (156)	Systematic review of RWE over the 2006/2007–2008/2009 and 2011/2012–2019/2020 influenza seasons (n = 11 analyses from nine 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 2018/2019 season

[a]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, randomized controlled trial; RT-PCR, reverse transcription PCR; rVE, relative vaccine efficacy/effectiveness; RWE, real-world evidence; SD, standard dose; TIIV, trivalent inactivated influenza virus vaccine; VE, vaccine efficacy/effectiveness.
[b]Primary outcome data only reported.
[c]N/A, not applicable.

technologies (179, 225, 226). 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, 225, 226).

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 to <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 to <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) vs 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 (221, 227, 228); 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 (227–229). First, the influenza HA gene is cloned into the baculovirus genome using homologous recombination (229). The resulting recombinant baculovirus is then transfected into insect cells (227–229).

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 (228). 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 (227).

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 (228), making them suitable for all people with egg allergy, including those who have experienced severe egg anaphylactic reactions.

TABLE 5 Overview of studies included in the review—live-attenuated influenza virus vaccines[a]

Citation/reference	Evidence type/study design	Vaccine investigated	Control/comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
Children and infants ≥6 months of age							
Morimoto et al. (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[c]
Boddington et al. (140)	Systematic review and meta-analysis of 37 test-negative studies published up to June 2020	LAIV	Not specified	Children 6 months to 17 years of age	Laboratory-confirmed influenza-associated hospitalization	N/A	VE of 44.3% (95% CI: 30.1, 55.7)
Children >2 years of age							
Mallory et al. (148)	Two RCTs in Japan during the 2014–2015 influenza season	LAIV (quadrivalent)	Study 1: uncontrolled single arm Study 2: Placebo	Children 2–6 years of age in study 1 (N = 100) and 7–18 years of age in study 2 (N = 1,301)	Laboratory (PCR)-confirmed influenza caused by vaccine-matched strains	Study 2: VE for vaccine-matched strains was 100% (95% CI: −1875.3, 100); VE for all influenza strains, regardless of match to the vaccine, was 27.5% (95% CI: 7.4, 43.0)	N/A
Jefferson et al. (164, 165)	Cochrane review of 41 RCTs published up to July 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 –16 years of age	
Mallory et al. (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. (147)	RCT in China during the 2016–2017 influenza season	LAIV	Placebo	Chinese children 3–17 years of age (N = 1,999)	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. (146)	RCT in rural India over 2 years (2015–2017)	LAIV	TIIV, placebo, or IPV	Children 2–10 years of age (N = 3,041)	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) 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)	Not reported
Children <18 years of age and adults and elderly adults ≥61 years of age							

(*Continued on next page*)

TABLE 5 Overview of studies included in the review—live-attenuated influenza virus vaccines[a] (*Continued*)

Citation/reference	Evidence type/study design	Vaccine investigated	Control/comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
Minozzi et al. (131)	Systematic review and meta-analysis of 220 RCTs published up to December 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

[a]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, randomized controlled trial; RR, relative risk; rRT-PCR, real-time reverse transcription PCR; RT-PCR, reverse transcription PCR; 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.
[b]Primary outcome data only reported.
[c]N/A, not applicable.

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) (230). 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-randomized observational study demonstrated a relative vaccine effectiveness against laboratory-confirmed influenza of 15.3% (95% CI: 5.9, 23.8) for recombinant QIIV vs 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 hospitalizations) in head-to-head randomized 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 to 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 (231) and is up to 100% for the prevention of meningococcal disease with meningococcal C conjugate vaccines (232). 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 (233). Vaccine effectiveness against influenza-related hospitalization 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) (233). 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 hospitalization (234). Therefore, there remains an unmet need for the development of additional technologies that may overcome some of the shortcomings associated with current technologies and

TABLE 6 Overview of studies included in the review—cell-based inactivated influenza virus vaccines (IIVcs)[a]

Citation/reference	Evidence type/study design	Vaccine investigated	Control/comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
Individuals ≥6 months of age							
Coleman et al. (162)	Systematic review and meta-analysis of RWE studies (*n* = 18) over three influenza seasons from 2017–2020	QIIVc	No vaccination, TIIVe, or QIIVe	Individuals ≥6 months of age	Laboratory-confirmed influenza	N/A[c]	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. (160)	Multicenter RCT across three influenza seasons from 2017 to 2019	QIIVc	Meningococcal ACWY vaccine	Children and adolescents 2 to <18 years of age (*N* = 4,514)	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. (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. (158, 161)	Systematic review of RCTs and non-randomized 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

[a]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, randomized controlled trial; RT-PCR, reverse transcription PCR; 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.
[b]Primary outcome data only reported.
[c]N/A, not applicable.

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 recombinant 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 the limitations of established vaccine platforms (235–237). DNA vaccines differ from the previously discussed recombinant vaccines in that they deliver DNA, rather than recombinant antigen (228, 235, 237). In 2021, a DNA plasmid-based SARS-CoV-2 vaccine (ZyCoV-D) was approved in India for active immunization to prevent COVID-19 in individuals ≥12 years of age (238–240), 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) (241). Processes involved in the production of mRNA vaccines vary, but typical steps are as follows: the antigen of interest is sequenced, and the optimized consensus sequence is used to create a linearized plasmid DNA template, which is then amplified and purified (241–243). This DNA template is then used as the basis for the synthesis of the target mRNA for the antigen by RNA polymerase enzymes (244). Finally, purified mRNAs are encapsulated into a lipid nanoparticle for delivery (245). A critical step for mRNA vaccine immunogenicity and efficacy is the incorporation of modified nucleotides (246), which can reduce the cell intrinsic response to the mRNA itself (247).

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 (248–251). 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 during the 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 (252–258). The results from a Phase 1 study of pandemic H1 DNA vaccine showed that it was well tolerated in healthy adults (24–70 years of age) (253). The H1 DNA vaccine demonstrated modest immunogenicity when administered as a single agent (prime vaccination) (253). DNA vaccines may also offer a potential strategy to improve the immunogenicity of current influenza virus vaccines, as evidenced in studies with influenza DNA vaccine prime followed by inactivated vaccine boost (257, 258). In Phase 1 clinical trial, H5 DNA priming followed by administration of a monovalent inactivated vaccine boost ≥12 weeks later, resulted in fourfold increases in hemagglutination inhibition (HAI) titer in 91% of recipients (257).

Several mRNA influenza virus vaccine candidates are currently being investigated (259–271). The final results of 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 (272). Lower doses of mRNA-1010 elicited generally higher (12.5 and 25 µg) or comparable (6.25 µg) titers to SD-IIV for influenza A virus strains but lower for influenza B strains (272). 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 (272). Phase 3 trials to assess the safety and efficacy of mRNA-1010 are ongoing (259, 260).

Two Phase 1, randomized, 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 (273). The vaccines were well tolerated and elicited robust humoral immune responses in healthy adults (273). 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 (274). 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 to induce long-lasting immune responses (275). 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 immunizations (274, 276).

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 fourfold increase in HAI titers in 83% of the participants after booster vaccination (277). Phases 1–3 clinical studies have been conducted for other infectious diseases (278), 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 (279). 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

Another new technology currently in development for influenza virus vaccines is recombinant virus-like particles (VLPs) prepared in mammalian, insect, and plant expression systems (280–282). The biological and morphological characteristics of recombinant VLPs are similar to the wild-type influenza virus (283), thus avoiding the drawbacks associated with antigenic drift. VLPs consist of a viral capsid without the core viral RNA required for replication (283). Therefore, although VLPs contain immunological epitopes and are highly immunogenic, they are not infectious (283).

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 (284). Results from a Phase 2, randomized, 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 (285). In two Phase 3 RCTs, a plant-derived VLP influenza virus vaccine demonstrated substantial protection against ILI compared with placebo in adults (282). 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 vs 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 vs an inactivated vaccine control was 8.8% (95% CI: −16.7, 28.7) (282).

Bi- and tri-pathogen immunization strategies

Combination vaccines reduce the number of injections required to protect against multiple diseases and may increase adherence to immunization schedules (286). Combination vaccines, for example, DTaP (diphtheria, tetanus toxoid, and acellular pertussis) and MMR (measles, mumps, and rubella) have long been available (286). 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 (287, 288), a Phase 3 trial successfully demonstrated greater efficacy at eliciting an immune response against both viruses in

TABLE 7 Overview of studies included in the review—recombinant influenza virus vaccines[a]

Citation/ reference	Evidence type/study design	Vaccine investigated	Control/ comparator	Study population	Primary study outcome	Key efficacy result(s)[b]	Key effectiveness result(s)[b]
Adults ≥18 years of age							
Evans et al. (159)	Phase 2b RCT during April and October 2019	MVA-NP+M1	Placebo (saline)	Non-immuno-suppressed adults ≥18 years of age who received the 2019 QIIV within 28 days of randomization (*N* = 2,152)	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[c]
Murchu et al. (158)	Systematic review of RCTs and non-randomized 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. (171)	Cluster-randomized 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) vs SD-QIIV in participants aged 50–64 years of age (*n* = 675,252)
Veroniki et al. (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) vs placebo (pairwise and network meta-analysis, *n* = 9 RCTs)	N/A

[a]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, randomized 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.
[b]Primary outcome data only reported.
[c]N/A, not applicable.

adults ≥50 years of age compared with vaccines that targeted only one (289, 290). Future developments may also include combination vaccines that offer protection from influenza, COVID-19, and respiratory syncytial virus (RSV) in a single formulation (286). Decisions regarding the strains of SARS-CoV-2 and influenza virus to be included in combination winter vaccines should be coordinated to optimize 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 (291–294). 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) (295). 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 candidates for universal influenza virus vaccines are in clinical development (296). 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 (295, 297). In addition to 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 (298).

A design of vaccines that are not pathogen specific was recently proposed using a concept termed "integrated organ immunity" (299). This involves innate and adaptive immune systems and non-hematopoietic cells interacting in tissue to elicit lasting, antigen-agnostic immunity (299).

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 (300). Seasonal influenza virus vaccination is effective at preventing illness and reducing the severity of the disease (48, 49, 301), and influenza virus vaccines have been widely used for over 60 years for the immunization 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 (77).

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 summarized 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 maximize 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 summarized are biased toward 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 hospitalizations. 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 immunization programs, 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 standardized 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 on strain matching, a process that may take approximately 6 months and can result in substantial morbidity and mortality before vaccine availability (121, 122).

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 program.

ACKNOWLEDGMENTS

Medical writing, under the guidance of the authors, was provided by Matthew Robinson DPhil from Inizio Medical, an Ashfield MedComms company, and was funded by Sanofi.

AUTHOR AFFILIATIONS

[1]School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[2]Department of Infectious Disease, Imperial College London, London, United Kingdom
[3]Sanofi, Reading, United Kingdom
[4]University of Nottingham School of Medicine, Nottingham, United Kingdom

AUTHOR ORCIDs

John S. Tregoning http://orcid.org/0000-0001-8093-8741
Helen Lister http://orcid.org/0000-0002-5958-4587

FUNDING

Funder	Grant(s)	Author(s)
Sanofi		John S. Tregoning
		Tristan W. Clark

Funder	Grant(s)	Author(s)
		Helen Lister
		Tiziano Poletti
		Jonathan S. Nguyen-Van-Tam
		Femy Amin

AUTHOR CONTRIBUTIONS

Tristan W. Clark, Methodology, Validation, Writing – review and editing | John S. Tregoning, Methodology, Validation, Writing – review and editing | Helen Lister, Conceptualization, Data curation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review and editing | Tiziano Poletti, Conceptualization, Data curation, Methodology, Validation, Writing – review and editing | Femy Amin, Conceptualization, Data curation, Methodology, Validation, Writing – review and editing | Jonathan S. Nguyen-Van-Tam, Methodology, Validation, Writing – review and editing

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplemental Material (CMR00025-24-s0001.docx). Table S1 (search strategy), Table S2 (eligibility criteria for selection of articles), Figure S1 (article selection flowchart).

REFERENCES

1. World Health Organization. 2023. Influenza (Seasonal) factsheet. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). Retrieved 8 Aug 2024.
2. Meier GC, Watkins J, McEwan P, Pockett RD. 2020. Resource use and direct medical costs of acute respiratory illness in the UK based on linked primary and secondary care records from 2001 to 2009. PLoS ONE 15:e0236472. https://doi.org/10.1371/journal.pone.0236472
3. Matias G, Taylor RJ, Haguinet F, Schuck-Paim C, Lustig RL, Fleming DM. 2016. Modelling estimates of age-specific influenza-related hospitalisation and mortality in the United Kingdom. BMC Public Health 16:481. https://doi.org/10.1186/s12889-016-3128-4
4. Moss JWE, Davidson C, Mattock R, Gibbons I, Mealing S, Carroll S. 2020. Quantifying the direct secondary health care cost of seasonal influenza in England. BMC Public Health 20:1464. https://doi.org/10.1186/s12889-020-09553-0
5. Maleki F, Welch V, Lopez SMC, Cane A, Langer J, Enstone A, Markus K, Wright O, Hewitt N, Whittle I. 2023. Understanding the global burden of influenza in adults aged 18-64 years: a systematic literature review from 2012 to 2022. Adv Ther 40:4166–4188. https://doi.org/10.1007/s12325-023-02610-1
6. GBD 2017 Influenza Collaborators. 2019. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 7:69–89.
7. World Health Organisation and Global Influenza Surveillance & Response System. 2023. Influenza laboratory surveillance information – virus detections by subtype reported to FluNet. Available from: https://app.powerbi.com/view?r=eyJrIjoiZTkyODcyO-TEtZjA5YS00ZmI0LWFkZGUtO-DIxNGI5OTE3YjM0IiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9. Retrieved 8 Aug 2024.
8. European Centre for Disease Prevention and Control. 2023. Seasonal influenza 2022–2023 annual epidemiological report for 2023., on ECDC. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/seasonal-influenza-annual-epidemiological-report-2022-2023.pdf. Retrieved 8 Aug 2024.
9. UK Health Security Agency. Surveillance of influenza and other seasonal respiratory viruses in the UK, winter 2022 to 2023. Available from: https://www.gov.uk/government/statistics/annual-flu-reports/surveillance-of-influenza-and-other-seasonal-respiratory-viruses-in-the-uk-winter-2022-to-2023#surveillance-of-influenza-and-seasonal-respiratory-viruses-in-the-uk. Retrieved 8 Aug 2024. Accessed August 8, 2024
10. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. 2014. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. J Infect 68:363–371. https://doi.org/10.1016/j.jinf.2013.11.013
11. GOV.UK. 2022. Influenza: the green book, chapter 19. Available from: https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19. Retrieved 8 Aug 2024.
12. Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, Fadel SA, Tran D, Fernandez E, Bhatnagar N, Loeb M. 2013. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 347:f5061. https://doi.org/10.1136/bmj.f5061
13. Sahni LC, Olson SM, Halasa NB, Stewart LS, Michaels MG, Williams JV, Englund JA, Klein EJ, Staat MA, Schlaudecker EP, Selvarangan R, Schuster JE, Weinberg GA, Szilagyi PG, Boom JA, Patel MM, Muñoz FM, New Vaccine Surveillance Network Collaborators. 2024. Maternal vaccine effectiveness against influenza-associated hospitalizations and emergency department visits in infants. JAMA Pediatr 178:176–184. https://doi.org/10.1001/jamapediatrics.2023.5639
14. Schuster JE, Hamdan L, Dulek DE, Kitko CL, Batarseh E, Haddadin Z, Stewart LS, Stahl A, Potter M, Rahman H, et al. 2023. Influenza vaccine in pediatric recipients of hematopoietic-cell transplants. N Engl J Med 388:374–376. https://doi.org/10.1056/NEJMc2210825
15. GOV.UK. 2023. Guidance. National flu immunisation programme 2023 to 2024 letter. Available from: https://www.gov.uk/government/publications/national-flu-immunisation-programme-plan/national-flu-immunisation-programme-2023-to-2024-letter. Retrieved 8 Aug 2024.
16. Wen T, Arditi B, Riley LE, Sobhani NC, Norton M, D'Alton M, Friedman AM, Venkatesh KK. 2021. Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United

States, 2000-2018. Obstet Gynecol 138:218–227. https://doi.org/10.1097/AOG.0000000000004462
17. Fell DB, Savitz DA, Kramer MS, Gessner BD, Katz MA, Knight M, Luteijn JM, Marshall H, Bhat N, Gravett MG, Skidmore B, Ortiz JR. 2017. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG 124:48–59. https://doi.org/10.1111/1471-0528.14143
18. UK Health Security Agency. 2023. Flu vaccination programme 2023 to 2024: information for healthcare practitioners. Available from: https://www.gov.uk/government/publications/flu-vaccination-programme-information-for-healthcare-practitioners/flu-vaccination-programme-2023-to-2024-information-for-healthcare-practitioners#contraindications-and-precautions. Retrieved 8 Aug 2024.
19. American College of Obstetricians and Gynecologists. 2024. Influenza in pregnancy: prevention and treatment: ACOG committee statement no. 7. Obstet Gynecol 143:e24–e30. https://doi.org/10.1097/AOG.0000000000005479
20. Wallick C, To TM, Korom S, Masters H, Hanania NA, Moawad D. 2022. Impact of influenza infection on the short- and long-term health of patients with chronic obstructive pulmonary disease. J Med Econ 25:930–939. https://doi.org/10.1080/13696998.2022.2098630
21. Macias AE, McElhaney JE, Chaves SS, Nealon J, Nunes MC, Samson SI, Seet BT, Weinke T, Yu H. 2021. The disease burden of influenza beyond respiratory illness. Vaccine (Auckl) 39 Suppl 1:A6–A14. https://doi.org/10.1016/j.vaccine.2020.09.048
22. Salomon A, Berry I, Tuite AR, Drews S, Hatchette T, Jamieson F, Johnson C, Kwong J, Lina B, Lojo J, Mosnier A, Ng V, Vanhems P, Fisman DN. 2020. Influenza increases invasive meningococcal disease risk in temperate countries. Clin Microbiol Infect 26:1257. https://doi.org/10.1016/j.cmi.2020.01.004
23. Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. 2015. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. Heart 101:1738–1747. https://doi.org/10.1136/heartjnl-2015-307691
24. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, Richardson DC, Rosella LC, Simor A, Smieja M, Zahariadis G, Gubbay JB. 2018. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 378:345–353. https://doi.org/10.1056/NEJMoa1702090
25. Blackburn R, Zhao H, Pebody R, Hayward A, Warren-Gash C. 2018. Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: time-series analysis of english data for 2004-2015. Clin Infect Dis 67:8–17. https://doi.org/10.1093/cid/cix1144
26. Andrew MK, MacDonald S, Godin J, McElhaney JE, LeBlanc J, Hatchette TF, Bowie W, Katz K, McGeer A, Semret M, McNeil SA. 2021. Persistent functional decline following hospitalization with influenza or acute respiratory illness. J Am Geriatr Soc 69:696–703. https://doi.org/10.1111/jgs.16950
27. Dawood FS, Kittikraisak W, Patel A, Rentz Hunt D, Suntarattiwong P, Wesley MG, Thompson MG, Soto G, Mundhada S, Arriola CS, et al. 2021. Incidence of influenza during pregnancy and association with pregnancy and perinatal outcomes in three middle-income countries: a multisite prospective longitudinal cohort study. Lancet Infect Dis 21:97–106. https://doi.org/10.1016/S1473-3099(20)30592-2
28. Omidi F, Zangiabadian M, Shahidi Bonjar AH, Nasiri MJ, Sarmastzadeh T. 2023. Influenza vaccination and major cardiovascular risk: a systematic review and meta-analysis of clinical trials studies. Sci Rep 13:20235. https://doi.org/10.1038/s41598-023-47690-9
29. Fröbert O, Götberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, Oldroyd KG, Motovska Z, Erglis A, Moer R, et al. 2021. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. Circulation 144:1476–1484. https://doi.org/10.1161/CIRCULATIONAHA.121.057042
30. Behrouzi B, Bhatt DL, Cannon CP, Vardeny O, Lee DS, Solomon SD, Udell JA. 2022. Association of influenza vaccination with cardiovascular risk: a meta-analysis. JAMA Netw Open 5:e228873. https://doi.org/10.1001/jamanetworkopen.2022.8873
31. Zhang R, Pang Y, Wan S, Lu M, Lv M, Wu J, Huang Y. 2022. Effectiveness of influenza vaccination on in-hospital death in older adults with respiratory diseases. Hum Vaccin Immunother 18:2117967. https://doi.org/10.1080/21645515.2022.2117967
32. Vamos EP, Pape UJ, Curcin V, Harris MJ, Valabhji J, Majeed A, Millett C. 2016. Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes. CMAJ 188:E342–E351. https://doi.org/10.1503/cmaj.151059
33. Centers for Disease Control and Prevention (CDC). Types of influenza viruses. Available from: https://www.cdc.gov/flu/about/viruses/types.htm. Retrieved 8 Aug 2024.
34. Sakai T, Nishimura SI, Naito T, Saito M. 2017. Influenza A virus hemagglutinin and neuraminidase act as novel motile machinery. Sci Rep 7:45043. https://doi.org/10.1038/srep45043
35. Wagner R, Matrosovich M, Klenk HD. 2002. Functional balance between haemagglutinin and neuraminidase in influenza virus infections. Rev Med Virol 12:159–166. https://doi.org/10.1002/rmv.352
36. Gaymard A, Le Briand N, Frobert E, Lina B, Escuret V. 2016. Functional balance between neuraminidase and haemagglutinin in influenza viruses. Clin Microbiol Infect 22:975–983. https://doi.org/10.1016/j.cmi.2016.07.007
37. Kosik I, Yewdell JW. 2019. Influenza hemagglutinin and neuraminidase: Yin–Yang proteins coevolving to thwart immunity. Viruses 11:346. https://doi.org/10.3390/v11040346
38. Johansson BE, Bucher DJ, Kilbourne ED. 1989. Purified influenza virus hemagglutinin and neuraminidase are equivalent in stimulation of antibody response but induce contrasting types of immunity to infection. J Virol 63:1239–1246. https://doi.org/10.1128/JVI.63.3.1239-1246.1989
39. Smith DJ, Lapedes AS, de Jong JC, Bestebroer TM, Rimmelzwaan GF, Osterhaus ADME, Fouchier RAM. 2004. Mapping the antigenic and genetic evolution of influenza virus. Science 305:371–376. https://doi.org/10.1126/science.1097211
40. Bean WJ, Schell M, Katz J, Kawaoka Y, Naeve C, Gorman O, Webster RG. 1992. Evolution of the H3 influenza virus hemagglutinin from human and nonhuman hosts. J Virol 66:1129–1138. https://doi.org/10.1128/JVI.66.2.1129-1138.1992
41. Webster RG, Laver WG, Air GM, Ward C, Gerhard W, van Wyke KL. 1980. The mechanism of antigenic drift in influenza viruses: analysis of Hong Kong (H3N2) variants with monoclonal antibodies to the hemagglutinin molecule. Ann N Y Acad Sci 354:142–161. https://doi.org/10.1111/j.1749-6632.1980.tb27964.x
42. Naeem A, Elbakkouri K, Alfaiz A, Hamed ME, Alsaran H, AlOtaiby S, Enani M, Alosaimi B. 2020. Antigenic drift of hemagglutinin and neuraminidase in seasonal H1N1 influenza viruses from Saudi Arabia in 2014 to 2015. J Med Virol 92:3016–3027. https://doi.org/10.1002/jmv.25759
43. Centers for Disease Control and Prevention (CDC). How flu viruses can change: "Drift" and "Shift. Available from: https://www.cdc.gov/flu/about/viruses/change.htm. Retrieved 8 Aug 2024.
44. Treanor J. 2004. Influenza vaccine--outmaneuvering antigenic shift and drift. N Engl J Med 350:218–220. https://doi.org/10.1056/NEJMp038238
45. Bouvier NM, Palese P. 2008. The biology of influenza viruses. Vaccine (Auckl) 26:D49–D53. https://doi.org/10.1016/j.vaccine.2008.07.039
46. Scholtissek C. 1994. Source for influenza pandemics. Eur J Epidemiol 10:455–458. https://doi.org/10.1007/BF01719674
47. Smith GJD, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, Ma SK, Cheung CL, Raghwani J, Bhatt S, Peiris JSM, Guan Y, Rambaut A. 2009. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature 459:1122–1125. https://doi.org/10.1038/nature08182
48. Kissling E, Maurel M, Emborg H-D, Whitaker H, McMenamin J, Howard J, Trebbien R, Watson C, Findlay B, Pozo F, Bolt Botnen A, Harvey C, Rose A, European IVE group, Members of the European IVE group. 2023. Interim 2022/23 influenza vaccine effectiveness: six European studies, October 2022 to January 2023. Euro Surveill 28:2300116. https://doi.org/10.2807/1560-7917.ES.2023.28.21.2300116
49. World Health Organization. 2022. Vaccines against influenza: WHO position paper – May 2022. Weekly Epidemiol Record 97
50. Chan TC, Fan-Ngai Hung I, Ka-Hay Luk J, Chu LW, Hon-Wai Chan F. 2014. Effectiveness of influenza vaccination in institutionalized older adults: a systematic review. J Am Med Dir Assoc 15:226. https://doi.org/10.1016/j.jamda.2013.10.008
51. Marano G, Boracchi P, Luconi E, Pariani E, Pellegrinelli L, Galli C, Gandolfi CE, Magoni M, Piro A, Scarcella C, Castaldi S, Biganzoli EM. 2021.

Evaluation of influenza vaccination efficacy in reducing influenza-related complications and excess mortality in Northern Italy (2014-2017). Expert Rev Vaccines 20:73–81. https://doi.org/10.1080/14760584.2021.1874927
52. Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. 2016. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. J Prev Med Hyg 57:E115–E120.
53. Smith W, Andrewes CH, Laidlaw PP. 1933. A virus obtained from influenza patients. The Lancet 222:66–68. https://doi.org/10.1016/S0140-6736(00)78541-2
54. Francis T. 1940. A new type of virus from epidemic influenza. Science 92:405–408. https://doi.org/10.1126/science.92.2392.405
55. Rozo M, Gronvall GK. 2015. The reemergent 1977 H1N1 strain and the gain-of-function debate. MBio 6:e01013-15. https://doi.org/10.1128/mBio.01013-15
56. Zhdanov VM, Lvov DK, Zakstelskaya LY, Yakhno MA, Isachenko VI, Braude NA, Reznik VI, Pysina TV, Andreyev VP, Podchernyaeva RY. 1978. Return of epidemic A1 (H1N1) influenza virus. Lancet 1:294–295. https://doi.org/10.1016/s0140-6736(78)90068-5
57. Public Health Service Advisory Committee. 1978. Influenza vaccine: recommendation of the public health service advisory committee on immunization practices. Ann Intern Med 89:657–659. https://doi.org/10.7326/0003-4819-89-5-657
58. Rota PA, Wallis TR, Harmon MW, Rota JS, Kendal AP, Nerome K. 1990. Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology (Auckl) 175:59–68. https://doi.org/10.1016/0042-6822(90)90186-u
59. Ambrose CS, Levin MJ. 2012. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother 8:81–88. https://doi.org/10.4161/hv.8.1.17623
60. Belshe RB. 2010. The need for quadrivalent vaccine against seasonal influenza. Vaccine (Auckl) 28 Suppl 4:D45–53. https://doi.org/10.1016/j.vaccine.2010.08.028
61. US Food and Drug Administration. 2023. Package insert - fluarix quadrivalent. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/fluarix-quadrivalent. Retrieved 8 Aug 2024.
62. Paget J, Caini S, Del Riccio M, van Waarden W, Meijer A. 2022. Has influenza B/Yamagata become extinct and what implications might this have for quadrivalent influenza vaccines? Euro Surveill 27:2200753. https://doi.org/10.2807/1560-7917.ES.2022.27.39.2200753
63. World Health Organization. 2023. Recommended composition of influenza virus vaccines for use in the 2024 southern hemisphere influenza season. Available from: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2024-southern-hemisphere-influenza-season. Retrieved 8 Aug 2024.
64. World Health Organization. 2023. Recommended composition of influenza virus vaccines for use in the 2023-2024 northern hemisphere influenza season. Available from: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2023-2024-northern-hemisphere-influenza-season. Retrieved 8 Aug 2024.
65. MedImmune. Highlights of prescribing information - FluMist Quadrivalent. Available from: https://www.fda.gov/media/160349/download. Retrieved 8 Aug 2024.
66. The Francis Crick Institute. Worldwide influenza centre lab. Available from: https://www.crick.ac.uk/research/platforms-and-facilities/worldwide-influenza-centre. Retrieved 8 Aug 2024.
67. World Health Organisation. 2021. Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Available from: https://iris.who.int/bitstream/handle/10665/341850/9789240024854-eng.pdf?sequence=1. Retrieved 8 Aug 2024.
68. Ziegler T, Moen A, Zhang W, Cox NJ. 2022. Global influenza surveillance and response system: 70 years of responding to the expected and preparing for the unexpected. Lancet 400:981–982. https://doi.org/10.1016/S0140-6736(22)01741-X
69. Public Health England. 2017. Influenza vaccine effectiveness (VE) in adults and children in primary care in the United Kingdom (UK): provisional end-of-season results 2017-18. Available from: https://assets.publishing.service.gov.uk/media/-5c6a8d3fed915d4a32cf05e8/Influenza_vaccine_effectiveness_in_primary_care_2017_2018.pdf. Retrieved 8 Aug 2024.
70. Public Health England. 2016. Influenza vaccine effectiveness (VE) in adults and children in primary care in the United Kingdom (UK): provisional end-of- season results 2016-17. Available from: https://assets.publishing.service.gov.uk/media/5c6a8d46e5274a72bdc02db0/Influenza_vaccine_effectiveness_in_primary_care_2016_2017.pdf. Retrieved 8 Aug 2024.
71. Public Health England. 2015. Influenza vaccine effectiveness in adults and children in primary care in the UK: provisional end-of-season results 2015-16. Available from: https://assets.publishing.service.gov.uk/media/5c6a8d4ced915d4a30a2e772/Influenza_vaccine_effectiveness_in_primary_care_2015_2016.pdf. Retrieved 8 Aug 2024.
72. Joint Committee on Vaccination and Immunisation. 2021. Advice on influenza vaccines for 2022/23. Available from: https://www.nitag-resource.org/sites/default/files/2021-10/JCVI%20Statement%20on%20Influenza%20Vaccines%202022-23.pdf. Retrieved 8 Aug 2024.
73. Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR, Talbot HK. 2023. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices — United States, 2023–24 influenza season. MMWR Recomm Rep 72:1–25. https://doi.org/10.15585/mmwr.rr7202a1
74. European Centre for Disease Prevention and Control. 2023. Seasonal influenza vaccination recommendations and coverage rates in EU/EEA Member States – An overview of vaccination recommendations for 2021−22 and coverage rates for the 2018–19 to 2020–21 influenza seasons. ECDC, Stockholm.
75. Joint Committee on Vaccination and Immunisation. 2018. Advice on influenza vaccines for 2019/20. Available from: https://app.box.com/s/t5ockz9bb6xw6t2mrrzb144njplimfo0/file/334815965677. Retrieved 8 Aug 2024.
76. Joint Committee on Vaccination and Immunisation. 2019. Advice on influenza vaccines for 2020/21. Available from: https://app.box.com/s/t5ockz9bb6xw6t2mrrzb144njplimfo0/file/529004924372. Retrieved 8 Aug 2024.
77. Joint Committee on Vaccination and Immunisation. 2023. Advice on influenza vaccines for 2023/24. Available from: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation. Retrieved 8 Aug 2024.
78. Principi N, Camilloni B, Esposito S, ESCMID Vaccine Study Group (EVASG). 2018. Influenza immunization policies: which could be the main reasons for differences among countries? Hum Vaccin Immunother 14:684–692. https://doi.org/10.1080/21645515.2017.1405188
79. World Health Organization. 2022. Guidance on an adapted evidence to recommendation process for national immunization technical advisory groups. World Health Organization. Available from: https://iris.who.int/handle/10665/356896. Retrieved 8 Aug 2024.
80. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ. 2013. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 66:719–725. https://doi.org/10.1016/j.jclinepi.2012.03.013
81. Joint Committee on Vaccination and Immunisation. 2013. The flu immunisation programme 2013/14 – extension to children. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/225360/Children_s_flu_letter_2013.pdf. Retrieved 8 Aug 2024.
82. Joint Committee on Vaccination and Immunisation. 2014. Childhood flu immunisation programme: update and provisional roll-out schedule. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/448915/2014-15_update_and_roll-out_schedule_letter.pdf. Retrieved 8 Aug 2024.
83. Public Health England. 2016. Extension of the Influenza immunisation programme to children in England. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/768945/Extension_of_the_Influenza_immunisation_programme_to_children_in_England.pdf. Retrieved 8 Aug 2024.

84. Atchison CJ, Hassounah S. 2015. The UK immunisation schedule: changes to vaccine policy and practice in 2013/14. JRSM Open 6:2054270415577762. https://doi.org/10.1177/2054270415577762
85. Kassianos G, MacDonald P, Aloysius I, Reynolds A. 2020. Implementation of the United Kingdom's childhood influenza national vaccination programme: a review of clinical impact and lessons learned over six influenza seasons. Vaccine (Auckl) 38:5747–5758. https://doi.org/10.1016/j.vaccine.2020.06.065
86. World Health Organization. 2023. Pandemic influenza preparedness framework: partnership contribution high-level implementation plan III 2024-2030. Available from: https://iris.who.int/bitstream/handle/10665/366981/9789240070141-eng.pdf?sequence=1. Retrieved 8 Aug 2024.
87. GOV.UK. 2020. UK pandemic preparedness. Available from: https://www.gov.uk/government/publications/uk-pandemic-preparedness/uk-pandemic-preparedness. Retrieved 8 Aug 2024.
88. HHS.gov. Objective 1: strategic implementation and deployment of the U.S. national pre-pandemic influenza vaccine stockpile (NPIVS). Available from: https://aspr.hhs.gov/legal/Pandemic-Influenza-Strategy/Pages/Objective-1.aspx. Retrieved 8 Aug 2024.
89. Australian Government Department of Health. 2019. Australian health management plan for pandemic influenza. Available from: https://www.health.gov.au/sites/default/files/documents/2022/05/australian-health-management-plan-for-pandemic-influenza-ahmppi.pdf. Retrieved 8 Aug 2024.
90. Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. 2021. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol 21:626–636. https://doi.org/10.1038/s41577-021-00592-1
91. Lurie N, Saville M, Hatchett R, Halton J. 2020. Developing covid-19 vaccines at pandemic speed. N Engl J Med 382:1969–1973. https://doi.org/10.1056/NEJMp2005630
92. GOV.UK. 2023. National risk register 2023 edition. Available from: https://assets.publishing.service.gov.uk/media/64ca1dfe19f5622669f3c1b1/2023_NATIONAL_RISK_REGISTER_NRR.pdf. Retrieved 8 Aug 2024.
93. Caserta LC, Frye EA, Butt SL, Laverack M, Nooruzzaman M, Covaleda LM, Thompson AC, Koscielny MP, Cronk B, Johnson A, Kleinhenz K, Edwards EE, Gomez G, Hitchener G, Martins M, Kapczynski DR, Suarez DL, Alexander Morris ER, Hensley T, Beeby JS, Lejeune M, Swinford AK, Elvinger F, Dimitrov KM, Diel DG. 2024. Spillover of highly pathogenic avian influenza H5N1 virus to dairy cattle. Nat New Biol. https://doi.org/10.1038/s41586-024-07849-4
94. Uyeki TM, Milton S, Abdul Hamid C, Reinoso Webb C, Presley SM, Shetty V, Rollo SN, Martinez DL, Rai S, Gonzales ER, Kniss KL, Jang Y, Frederick JC, De La Cruz JA, Liddell J, Di H, Kirby MK, Barnes JR, Davis CT. 2024. Highly pathogenic avian influenza A(H5N1) virus infection in a dairy farm worker. N Engl J Med 390:2028–2029. https://doi.org/10.1056/NEJMc2405371
95. Neumann G, Kawaoka Y. 2024. Highly pathogenic H5N1 avian influenza virus outbreak in cattle: the knowns and unknowns. Nat Rev Microbiol 22:525–526. https://doi.org/10.1038/s41579-024-01087-1
96. Eisfeld AJ, Biswas A, Guan L, Gu C, Maemura T, Trifkovic S, Wang T, Babujee L, Dahn R, Halfmann PJ, Barnhardt T, Neumann G, Suzuki Y, Thompson A, Swinford AK, Dimitrov KM, Poulsen K, Kawaoka Y. 2024. Pathogenicity and transmissibility of bovine H5N1 influenza virus. Nature. https://doi.org/10.1038/s41586-024-07766-6
97. Mahase E. 2024. Bird flu: Australia records first human case of H5N1. BMJ 385:q1281. https://doi.org/10.1136/bmj.q1281
98. Looi MK. 2024. Bird flu: US confirms first case with respiratory symptoms. BMJ 385:q1203. https://doi.org/10.1136/bmj.q1203
99. Centers for Disease Control and Prevention (CDC). 2024. U.S. case of human avian influenza A(H5) virus reported. Available from: https://www.cdc.gov/media/releases/2022/s0428-avian-flu.html. Retrieved 8 Aug 2024.
100. Centers for Disease Control and Prevention. 2024. H5N1 Bird Flu: current situation. Available from: https://www.cdc.gov/bird-flu/situation-summary/index.html. Retrieved 8 Aug 2024.
101. Centers for Disease Control and Prevention (CDC). 2024. CDC A(H5N1) bird flu response update, July 12, 2024. Available from: https://www.cdc.gov/bird-flu/spotlights/h5n1-response-07122024.html. Retrieved 8 Aug 2024.
102. European Centre for Disease Prevention and Control. 2024. Avian flu: increased vigilance recommended. Available from: https://www.ecdc.europa.eu/en/news-events/avian-flu-increased-vigilance-recommended. Retrieved 8 Aug 2024.
103. UK Health Security Agency. 2023. Investigation into the risk to human health of avian influenza (influenza A H5N1) in England: technical briefing 5. Available from: https://www.gov.uk/government/publications/avian-influenza-influenza-a-h5n1-technical-briefings/investigation-into-the-risk-to-human-health-of-avian-influenza-influenza-a-h5n1-in-england-technical-briefing-5. Retrieved 8 Aug 2024.
104. Cargnin Faccin F, Perez DR. 2024. Pandemic preparedness through vaccine development for avian influenza viruses. Hum Vaccin Immunother 20:2347019. https://doi.org/10.1080/21645515.2024.2347019
105. Chen J-R, Liu Y-M, Tseng Y-C, Ma C. 2020. Better influenza vaccines: an industry perspective. J Biomed Sci 27:33. https://doi.org/10.1186/s12929-020-0626-6
106. AstraZeneca UK Limited. Influenza vaccine (live attenuated, nasal). Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/3296/smpc/print. Retrieved 8 Aug 2024.
107. Mylan. Influenza virus (surface antigen, inactivated). Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/9381/smpc/print. Retrieved 8 Aug 2024.
108. Sanofi. Quadrivalent influenza vaccine (split virion, inactivated). Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/666/smpc/print. Retrieved 8 Aug 2024.
109. Sanofi. Quadrivalent influenza vaccine (recombinant, prepared in cell culture). Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/12761/smpc/print. Retrieved 8 Aug 2024.
110. Seqirus UK Limited. Adjuvanted quadrivalent influenza vaccine (surface antigen, inactivated). Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/12881/smpc/print. Retrieved 8 Aug 2024.
111. Seqirus UK Limited. Cell-based quadrivalent Influenza vaccine (surface antigen, inactivated). Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/12882/smpc/print. Retrieved 8 Aug 2024.
112. UK Health Security Agency. 2023. All influenza vaccines marketed in the UK for the 2023 to 2024 season (text version). Available from: https://www.gov.uk/government/publications/influenza-vaccines-marketed-in-the-uk/all-influenza-vaccines-marketed-in-the-uk-for-the-2022-to-2023-season. Retrieved 8 Aug 2024.
113. Demirden SF, Alptekin K, Kimiz-Gebologlu I, Oncel SS. 2022. Influenza vaccine: an engineering vision from virological importance to production. Biotechnol Bioprocess Eng 27:714–738. https://doi.org/10.1007/s12257-022-0115-8
114. Chan L, Alizadeh K, Alizadeh K, Fazel F, Kakish JE, Karimi N, Knapp JP, Mehrani Y, Minott JA, Morovati S, Rghei A, Stegelmeier AA, Vanderkamp S, Karimi K, Bridle BW. 2021. Review of influenza virus vaccines: the qualitative nature of immune responses to infection and vaccination is a critical consideration. Vaccines (Basel) 9:979. https://doi.org/10.3390/vaccines9090979
115. Mascola JR, Fauci AS. 2020. Novel vaccine technologies for the 21st century. Nat Rev Immunol 20:87–88. https://doi.org/10.1038/s41577-019-0243-3
116. Nuwarda RF, Alharbi AA, Kayser V. 2021. An overview of influenza viruses and vaccines. Vaccines 9:1032. https://doi.org/10.3390/vaccines9091032
117. Leong SL, Gras S, Grant EJ. 2024. Fighting flu: novel CD8$^+$ T-cell targets are required for future influenza vaccines. Clin Transl Immunol 13:e1491. https://doi.org/10.1002/cti2.1491
118. World Health Organisation (WHO). Global influenza programme: surveillance & monitoring. Available from: https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/influenza#:~:text=ILI%20case%20definition,within%20the%20last%2010%20days. Retrieved 8 Aug 2024.
119. Centers for Disease Control and Prevention (CDC). Glossary of influenza (Flu) terms. Available from: https://www.cdc.gov/flu/about/glossary.htm. Retrieved 8 Aug 2024.
120. Wood JM, Major D, Heath A, Newman RW, Höschler K, Stephenson I, Clark T, Katz JM, Zambon MC. 2012. Reproducibility of serology assays

for pandemic influenza H1N1: collaborative study to evaluate a candidate WHO International Standard. Vaccine (Auckl) 30:210–217. https://doi.org/10.1016/j.vaccine.2011.11.019
121. Krammer F, Weir JP, Engelhardt O, Katz JM, Cox RJ. 2020. Meeting report and review: immunological assays and correlates of protection for next-generation influenza vaccines. Influenza Other Respir Viruses 14:237–243. https://doi.org/10.1111/irv.12706
122. Plotkin SA. 2010. Correlates of protection induced by vaccination. Clin Vaccine Immunol 17:1055–1065. https://doi.org/10.1128/CVI.00131-10
123. Loeb M, Roy A, Dokainish H, Dans A, Palileo-Villanueva LM, Karaye K, Zhu J, Liang Y, Goma F, Damasceno A, Alhabib KF, Yonga G, Mondo C, Almahmeed W, Al Mulla A, Thanabalan V, Rao-Melacini P, Grinvalds A, McCready T, Bangdiwala SI, Yusuf S, Influenza Vaccine to Prevent Adverse Vascular Events investigators. 2022. Influenza vaccine to reduce adverse vascular events in patients with heart failure: a multinational randomised, double-blind, placebo-controlled trial. Lancet Glob Health 10:e1835–e1844. https://doi.org/10.1016/S2214-109X(22)00432-6
124. Fonseca HAR, Furtado RHM, Zimerman A, Lemos PA, Franken M, Monfardini F, Pedrosa RP, Patriota R de LS, Passos LCS, Dall'Orto FTC, et al. 2022. Influenza vaccination strategy in acute coronary syndromes: the VIP-ACS trial. Eur Heart J 43:4378–4388. https://doi.org/10.1093/eurheartj/ehac472
125. Vardeny O, Kim K, Udell JA, Joseph J, Desai AS, Farkouh ME, Hegde SM, Hernandez AF, McGeer A, Talbot HK, et al. 2021. Effect of high-dose trivalent vs standard-dose quadrivalent influenza vaccine on mortality or cardiopulmonary hospitalization in patients with high-risk cardiovascular disease: a randomized clinical trial. JAMA 325:39–49. https://doi.org/10.1001/jama.2020.23649
126. Fröbert O, Götberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, Oldroyd KG, Motovska Z, Erglis A, Moer R, et al. 2023. Clinical impact of influenza vaccination after ST- and non-ST-segment elevation myocardial infarction - insights from the IAMI trial. Am Heart J 255:82–89. https://doi.org/10.1016/j.ahj.2022.10.005
127. Verhees RAF, Thijs C, Ambergen T, Dinant GJ, Knottnerus JA. 2019. Influenza vaccination in the elderly: 25 years follow-up of a randomized controlled trial. No impact on long-term mortality. PLoS ONE 14:e0216983. https://doi.org/10.1371/journal.pone.0216983
128. Bitterman R, Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. 2018. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2:CD008983. https://doi.org/10.1002/14651858.CD008983.pub3
129. Palmu AA, Pepin S, Syrjänen RK, Mari K, Mallett Moore T, Jokinen J, Nieminen H, Kilpi T, Samson SI, De Bruijn I. 2024. High-dose quadrivalent influenza vaccine for prevention of cardiovascular and respiratory hospitalizations in older adults. Influenza Other Respir Viruses 18:e13270. https://doi.org/10.1111/irv.13270
130. Peikert A, Claggett BL, Udell JA, Joseph J, Hegde SM, Kim K, Mao L, Wang T, Havighurst TC, Farkouh ME, Bhatt DL, Tattersall MC, Cooper LS, Solomon SD, Vardeny O. 2024. Influenza vaccine immune response in patients with high-risk cardiovascular disease: a secondary analysis of the INVESTED randomized clinical trial. JAMA Cardiol 9:574–581. https://doi.org/10.1001/jamacardio.2024.0468
131. Minozzi S, Lytras T, Gianola S, Gonzalez-Lorenzo M, Castellini G, Galli C, Cereda D, Bonovas S, Pariani E, Moja L. 2022. Comparative efficacy and safety of vaccines to prevent seasonal influenza: a systematic review and network meta-analysis. E Clin Med 46:101331. https://doi.org/10.1016/j.eclinm.2022.101331
132. Lee JKH, Lam GKL, Shin T, Samson SI, Greenberg DP, Chit A. 2021. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. Vaccine (Auckl) 39 Suppl 1:A24–A35. https://doi.org/10.1016/j.vaccine.2020.09.004
133. Jarvis JR, Dorey RB, Warricker FDM, Alwan NA, Jones CE. 2020. The effectiveness of influenza vaccination in pregnancy in relation to child health outcomes: systematic review and meta-analysis. Vaccine (Auckl) 38:1601–1613. https://doi.org/10.1016/j.vaccine.2019.12.056
134. Wall DJ, Patel MM, Chung J, Lee B, Dawood FS. 2021. Antibody response and protection after receipt of inactivated influenza vaccine: a systematic review. Pediatrics 147:e2020019901. https://doi.org/10.1542/peds.2020-019901
135. Dbaibo G, Amanullah A, Claeys C, Izu A, Jain VK, Kosalaraksa P, Rivera L, Soni J, Yanni E, Zaman K, et al. 2020. Quadrivalent influenza vaccine prevents illness and reduces healthcare utilization across diverse geographic regions during five influenza seasons: a randomized clinical trial. Pediatr Infect Dis J 39:e1–e10. https://doi.org/10.1097/INF.0000000000002504
136. Esposito S, Nauta J, Lapini G, Montomoli E, van de Witte S. 2022. Efficacy and safety of a quadrivalent influenza vaccine in children aged 6-35 months: a global, multiseasonal, controlled, randomized phase III study. Vaccine (Auckl) 40:2626–2634. https://doi.org/10.1016/j.vaccine.2022.02.088
137. Danier J, Rivera L, Claeys C, Dbaibo G, Jain VK, Kosalaraksa P, Woo W, Yanni E, Zaman K, Acosta B, et al. 2019. Clinical presentation of influenza in children 6 to 35 months of age: findings from a randomized clinical trial of inactivated quadrivalent influenza vaccine. Pediatr Infect Dis J 38:866–872. https://doi.org/10.1097/INF.0000000000002387
138. Pepin S, Dupuy M, Borja-Tabora CFC, Montellano M, Bravo L, Santos J, de Castro J-A, Rivera-Medina DM, Cutland C, Ariza M, Diez-Domingo J, Gonzalez CD, Martinón-Torres F, Papadopoulou-Alataki E, Theodoriadou M, Kazek-Duret MP, Gurunathan S, De Bruijn I, GQM05 Study Group. 2019. Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6-35 months: a multiseason randomised placebo-controlled trial in the Northern and Southern Hemispheres. Vaccine (Auckl) 37:1876–1884. https://doi.org/10.1016/j.vaccine.2018.11.074
139. Claeys C, Zaman K, Dbaibo G, Li P, Izu A, Kosalaraksa P, Rivera L, Acosta B, Arroba Basanta ML, Aziz A, et al. 2018. Prevention of vaccine-matched and mismatched influenza in children aged 6-35 months: a multinational randomised trial across five influenza seasons. Lancet Child Adolesc Health 2:338–349. https://doi.org/10.1016/S2352-4642(18)30062-2
140. Boddington NL, Pearson I, Whitaker H, Mangtani P, Pebody RG. 2021. Effectiveness of influenza vaccination in preventing hospitalization due to influenza in children: a systematic review and meta-analysis. Clin Infect Dis 73:1722–1732. https://doi.org/10.1093/cid/ciab270
141. Mallory RM, Bandell A, Ambrose CS, Yu J. 2020. A systematic review and meta-analysis of the effectiveness of LAIV4 and IIV in children aged 6 months to 17 years during the 2016-2017 season. Vaccine (Auckl) 38:3405–3410. https://doi.org/10.1016/j.vaccine.2019.12.015
142. Omer SB, Clark DR, Madhi SA, Tapia MD, Nunes MC, Cutland CL, Simões EAF, Aqil AR, Katz J, Tielsch JM, Steinhoff MC, Wairagkar N, BMGF Supported Maternal Influenza Immunization Trials Investigators Group. 2020. Efficacy, duration of protection, birth outcomes, and infant growth associated with influenza vaccination in pregnancy: a pooled analysis of three randomised controlled trials. Lancet Respir Med 8:597–608. https://doi.org/10.1016/S2213-2600(19)30479-5
143. Niang MN, Sugimoto JD, Diallo A, Diarra B, Ortiz JR, Lewis KDC, Lafond KE, Halloran ME, Widdowson M-A, Neuzil KM, Victor JC. 2021. Estimates of inactivated influenza vaccine effectiveness among children in senegal: results from 2 consecutive cluster-randomized controlled trials in 2010 and 2011. Clin Infect Dis 72:e959–e969. https://doi.org/10.1093/cid/ciaa1689
144. Diallo A, Diop OM, Diop D, Niang MN, Sugimoto JD, Ortiz JR, Faye EHA, Diarra B, Goudiaby D, Lewis KDC, Emery SL, Zangeneh SZ, Lafond KE, Sokhna C, Halloran ME, Widdowson M-A, Neuzil KM, Victor JC. 2019. Effectiveness of seasonal influenza vaccination in children in senegal during a year of vaccine mismatch: a cluster-randomized trial. Clin Infect Dis 69:1780–1788. https://doi.org/10.1093/cid/ciz066
145. Sullender WM, Fowler KB, Gupta V, Krishnan A, Ram Purakayastha D, Srungaram Vln R, Lafond KE, Saha S, Palomeque FS, Gargiullo P, Jain S, Lal R, Widdowson MA, Broor S. 2019. Efficacy of inactivated trivalent influenza vaccine in rural India: a 3-year cluster-randomised controlled trial. Lancet Glob Health 7:e940–e950. https://doi.org/10.1016/S2214-109X(19)30079-8
146. Krishnan A, Dar L, Saha S, Narayan VV, Kumar R, Kumar R, Amarchand R, Dhakad S, Chokker R, Choudekar A, Gopal G, Choudhary A, Potdar V, Chadha M, Lafond KE, Lindstrom S, Widdowson M-A, Jain S. 2021. Efficacy of live attenuated and inactivated influenza vaccines among children in rural India: A 2-year, randomized, triple-blind, placebo-controlled trial. PLoS Med 18:e1003609. https://doi.org/10.1371/journal.pmed.1003609
147. Wang S, Zheng Y, Jin X, Gan Z, Shao Y, Zhu C, Hu X, Liang Z, Chen Y, Xing B, Lv H, Xu N. 2020. Efficacy and safety of a live attenuated influenza vaccine in Chinese healthy children aged 3-17 years in one study center of a randomized, double-blind, placebo-controlled phase 3 clinical trial, 2016/17 season. Vaccine (Auckl) 38:5979–5986. https://doi.org/10.1016/j.vaccine.2020.07.019

148. Mallory RM, Yu J, Kameo S, Tanaka M, Rito K, Itoh Y, Dubovsky F. 2018. The safety and efficacy of quadrivalent live attenuated influenza vaccine in Japanese children aged 2-18 years: results of two phase 3 studies. Influenza Other Respir Viruses 12:438–445. https://doi.org/10.1111/irv.12555
149. Morimoto N, Takeishi K. 2018. Change in the efficacy of influenza vaccination after repeated inoculation under antigenic mismatch: a systematic review and meta-analysis. Vaccine (Auckl) 36:949–957. https://doi.org/10.1016/j.vaccine.2018.01.023
150. Lee JKH, Lam GKL, Yin JK, Loiacono MM, Samson SI. 2023. High-dose influenza vaccine in older adults by age and seasonal characteristics: systematic review and meta-analysis update. Vaccine X 14:100327. https://doi.org/10.1016/j.jvacx.2023.100327
151. Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, Chit A. 2018. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines 17:435–443. https://doi.org/10.1080/14760584.2018.1471989
152. Leibovici Weissman Y, Cooper L, Sternbach N, Ashkenazi-Hoffnung L, Yahav D. 2021. Clinical efficacy and safety of high dose trivalent influenza vaccine in adults and immunosuppressed populations - a systematic review and meta-analysis. J Infect 83:444–451. https://doi.org/10.1016/j.jinf.2021.08.028
153. Vesikari T, Kirstein J, Devota Go G, Leav B, Ruzycky ME, Isakov L, de Bruijn M, Oberye J, Heijnen E. 2018. Efficacy, immunogenicity, and safety evaluation of an MF59-adjuvanted quadrivalent influenza virus vaccine compared with non-adjuvanted influenza vaccine in children: a multicentre, randomised controlled, observer-blinded, phase 3 trial. Lancet Respir Med 6:345–356. https://doi.org/10.1016/S2213-2600(18)30108-5
154. Loeb M, Russell ML, Kelly-Stradiotto C, Fuller N, Fonseca K, Earn DJD, Chokani K, Babiuk L, Neupane B, Singh P, Pullenayegum E. 2021. Adjuvanted trivalent influenza vaccine versus quadrivalent inactivated influenza vaccine in Hutterite Children: a randomized clinical trial. Vaccine (Auckl) 39:6843–6851. https://doi.org/10.1016/j.vaccine.2021.10.035
155. Domnich A, de Waure C. 2022. Comparative effectiveness of adjuvanted versus high-dose seasonal influenza vaccines for older adults: a systematic review and meta-analysis. Int J Infect Dis 122:855–863. https://doi.org/10.1016/j.ijid.2022.07.048
156. Gärtner BC, Weinke T, Wahle K, Kwetkat A, Beier D, Schmidt KJ, Schwarz TF. 2022. Importance and value of adjuvanted influenza vaccine in the care of older adults from a European perspective - a systematic review of recently published literature on real-world data. Vaccine (Auckl) 40:2999–3008. https://doi.org/10.1016/j.vaccine.2022.04.019
157. Coleman BL, Sanderson R, Haag MDM, McGovern I. 2021. Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis. Influenza Other Respir Viruses 15:813–823. https://doi.org/10.1111/irv.12871
158. O Murchu E, Comber L, Jordan K, Hawkshaw S, Marshall L, O'Neill M, Ryan M, Teljeur C, Carnahan A, Pérez JJ, Robertson AH, Johansen K, Jonge J de, Krause T, Nicolay N, Nohynek H, Pavlopoulou I, Pebody R, Penttinen P, Soler‐Soneira M, Wichmann O, Harrington P. 2023. Systematic review of the efficacy, effectiveness and safety of recombinant haemagglutinin seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Rev Med Virol 33:e2331. https://doi.org/10.1002/rmv.2331
159. Evans TG, Bussey L, Eagling-Vose E, Rutkowski K, Ellis C, Argent C, Griffin P, Kim J, Thackwray S, Shakib S, Doughty J, Gillies J, Wu J, Druce J, Pryor M, Gilbert S. 2022. Efficacy and safety of a universal influenza A vaccine (MVA-NP+M1) in adults when given after seasonal quadrivalent influenza vaccine immunisation (FLU009): a phase 2b, randomised, double-blind trial. Lancet Infect Dis 22:857–866. https://doi.org/10.1016/S1473-3099(21)00702-7
160. Nolan T, Fortanier AC, Leav B, Põder A, Bravo LC, Szymański HT, Heeringa M, Vermeulen W, Matassa V, Smolenov I, Edelman JM. 2021. Efficacy of a cell-culture-derived quadrivalent influenza vaccine in children. N Engl J Med 385:1485–1495. https://doi.org/10.1056/NEJMoa2024848
161. Jordan K, Murchu EO, Comber L, Hawkshaw S, Marshall L, O'Neill M, Teljeur C, Harrington P, Carnahan A, Pérez-Martín JJ, Robertson AH, Johansen K, Jonge J de, Krause T, Nicolay N, Nohynek H, Pavlopoulou I, Pebody R, Penttinen P, Soler-Soneira M, Wichmann O, Ryan M. 2023. Systematic review of the efficacy, effectiveness and safety of cell-based seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Rev Med Virol 33:e2332. https://doi.org/10.1002/rmv.2332
162. Coleman BL, Gutmanis I, McGovern I, Haag M. 2023. Effectiveness of cell-based quadrivalent seasonal influenza vaccine: a systematic review and meta-analysis. Vaccines (Basel) 11:1607. https://doi.org/10.3390/vaccines11101607
163. Puig-Barberà J, Tamames-Gómez S, Plans-Rubio P, Eiros-Bouza JM. 2022. Relative effectiveness of cell-cultured versus egg-based seasonal influenza vaccines in preventing influenza-related outcomes in subjects 18 years old or older: a systematic review and meta-analysis. Int J Environ Res Public Health 19:818. https://doi.org/10.3390/-ijerph19020818
164. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. 2018. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2:CD001269. https://doi.org/10.1002/14651858.CD001269.pub6
165. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. 2018. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2:CD004879. https://doi.org/10.1002/14651858.CD004879.pub5
166. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. 2018. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2:CD004876. https://doi.org/10.1002/14651858.CD004876.pub4
167. O Murchu E, Comber L, Jordan K, Hawkshaw S, Marshall L, O'Neill M, Ryan M, Teljeur C, Carnahan A, Pérez JJ, Robertson AH, Johansen K, Jonge J de, Krause T, Nicolay N, Nohynek H, Pavlopoulou I, Pebody R, Penttinen P, Soler‐Soneira M, Wichmann O, Harrington P. 2023. Systematic review of the efficacy, effectiveness and safety of MF59 adjuvanted seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Rev Med Virol 33:e2329. https://doi.org/10.1002/rmv.2329
168. Comber L, O Murchu E, Jordan K, Hawkshaw S, Marshall L, O'Neill M, Teljeur C, Ryan M, Carnahan A, Pérez Martín JJ, Robertson AH, Johansen K, de Jonge J, Krause T, Nicolay N, Nohynek H, Pavlopoulou I, Pebody R, Penttinen P, Soler-Soneira M, Wichmann O, Harrington P. 2023. Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Rev Med Virol 33:e2330. https://doi.org/10.1002/rmv.2330
169. Veroniki AA, Thirugnanasampanthar SS, Konstantinidis M, Dourka J, Ghassemi M, Neupane D, Khan P, Nincic V, Corry M, Robson R, et al. 2024. Trivalent and quadrivalent seasonal influenza vaccine in adults aged 60 and older: a systematic review and network meta-analysis. BMJ Evid Based Med 29:239–254. https://doi.org/10.1136/bmjebm-2023-112767
170. Skaarup KG, Lassen MCH, Modin D, Johansen ND, Loiacono MM, Harris RC, Lee JKH, Dufournet M, Vardeny O, Peikert A, Claggett B, Solomon SD, Jensen JUS, Biering-Sørensen T. 2024. The relative vaccine effectiveness of high-dose vs standard-dose influenza vaccines in preventing hospitalization and mortality: a meta-analysis of evidence from randomized trials. J Infect 89:106187. https://doi.org/10.1016/j.jinf.2024.106187
171. Hsiao A, Yee A, Fireman B, Hansen J, Lewis N, Klein NP. 2023. Recombinant or standard-dose influenza vaccine in adults under 65 years of age. N Engl J Med 389:2245–2255. https://doi.org/10.1056/NEJMoa2302099
172. Ernst E, Pittler MH. 2006. Efficacy or effectiveness? J Intern Med 260:488–490. https://doi.org/10.1111/j.1365-2796.2006.01707.x
173. Weinberg GA, Szilagyi PG. 2010. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. J Infect Dis 201:1607–1610. https://doi.org/10.1086/652404
174. Nogales A, Martínez-Sobrido L. 2016. Reverse genetics approaches for the development of influenza vaccines. Int J Mol Sci 18:20. https://doi.org/10.3390/ijms18010020
175. President's Council of Advisors on Science and Technology. Report to the president on reengeneering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. Accessed August 8, 2024. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf.
176. Pérez-Rubio A, Ancochea J, Eiros Bouza JM. 2020. Quadrivalent cell culture influenza virus vaccine. Comparison to egg-derived vaccine.

Hum Vaccin Immunother 16:1746–1752. https://doi.org/10.1080/21645515.2019.1701912
177. Meng D, Hui Z, Yang J, Yuan J, Ling Y, He C. 2009. Reduced egg production in hens associated with avian influenza vaccines and formalin levels. Avian Dis 53:16–20. https://doi.org/10.1637/8343-050208-Reg.1
178. Harding AT, Heaton NS. 2018. Efforts to improve the seasonal influenza vaccine. Vaccines (Basel) 6:19. https://doi.org/10.3390/vaccines6020019
179. Park YW, Kim YH, Jung HU, Jeong OS, Hong EJ, Kim H, Lee JI. 2020. Comparison of antigenic mutation during egg and cell passage cultivation of H3N2 influenza virus. Clin Exp Vaccine Res 9:56–63. https://doi.org/10.7774/cevr.2020.9.1.56
180. Robertson JS, Bootman JS, Newman R, Oxford JS, Daniels RS, Webster RG, Schild GC. 1987. Structural changes in the haemagglutinin which accompany egg adaptation of an influenza A(H1N1) virus. Virology (Auckl) 160:31–37. https://doi.org/10.1016/0042-6822(87)90040-7
181. Skowronski DM, Janjua NZ, De Serres G, Sabaiduc S, Eshaghi A, Dickinson JA, Fonseca K, Winter A-L, Gubbay JB, Krajden M, Petric M, Charest H, Bastien N, Kwindt TL, Mahmud SM, Van Caeseele P, Li Y. 2014. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. PLoS ONE 9:e92153. https://doi.org/10.1371/journal.pone.0092153
182. Zost SJ, Parkhouse K, Gumina ME, Kim K, Diaz Perez S, Wilson PC, Treanor JJ, Sant AJ, Cobey S, Hensley SE. 2017. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci U S A 114:12578–12583. https://doi.org/10.1073/pnas.1712377114
183. Chatterjee A, Ambrose K, Canaday DH, Delair S, Ezike N, Huber VC, Jhaveri R, Nyquist AC, Sporer A, Varman M, Vivekanandan R, Wojcik R, Jandhyala R. 2024. The association between influenza vaccine effectiveness and egg-based manufacturing technology: literature review and US expert consensus. Curr Med Res Opin 40:335–343. https://doi.org/10.1080/03007995.2023.2284386
184. Liang W, Tan TJC, Wang Y, Lv H, Sun Y, Bruzzone R, Mok CKP, Wu NC. 2022. Egg-adaptive mutations of human influenza H3N2 virus are contingent on natural evolution. PLoS Pathog 18:e1010875. https://doi.org/10.1371/journal.ppat.1010875
185. Montomoli E, Wojcik R, Christopher S, Mosnier A, Pariani E, Trilla Garcia A, Fickenscher H, Gärtner BC, Jandhyala R, Zambon M, Moore C, Ortiz de Lejarazu-LeonardoR. 2021. Estimation of reduction in influenza vaccine effectiveness due to egg-adaptation changes-systematic literature review and expert consensus. Vaccines (Basel) 9:1255. https://doi.org/10.3390/vaccines9111255
186. Des Roches A, Paradis L, Gagnon R, Lemire C, Bégin P, Carr S, Chan ES, Paradis J, Frenette L, Ouakki M, Benoît M, De Serres G, PCIRN (Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network). 2012. Egg-allergic patients can be safely vaccinated against influenza. J Allergy Clin Immunol 130:1213–1216. https://doi.org/10.1016/j.jaci.2012.07.046
187. Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M, SNIFFLE-2 Study Investigators. 2015. Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study. BMJ 351:h6291. https://doi.org/10.1136/bmj.h6291
188. Sabbaghi A, Miri SM, Keshavarz M, Zargar M, Ghaemi A. 2019. Inactivation methods for whole influenza vaccine production. Rev Med Virol 29:e2074. https://doi.org/10.1002/rmv.2074
189. Gomez PL, Robinson JM, Rogalewicz JA. 2013. Vaccine manufacturing. Vaccines (Basel):44–57. https://doi.org/10.1016/B978-1-4557-0090-5.00019-7
190. Australian Government Department of Health. 2023. Statement on the administration of seasonal influenza vaccines in 2023. Available from: https://www.health.gov.au/sites/default/files/2023-06/atagi-advice-on-seasonal-influenza-vaccines-in-2023_0.pdf. Retrieved 8 Aug 2024.
191. Manatū Hauora Ministry of Health. 2020. Immunisation handbook 2020. 11. Influenza. Available from: https://www.health.govt.nz/our-work/immunisation-handbook-2020/11-influenza#10-4. Retrieved 8 Aug 2024.
192. Dugan HL, Henry C, Wilson PC. 2020. Aging and influenza vaccine-induced immunity. Cell Immunol 348:103998. https://doi.org/10.1016/j.cellimm.2019.103998
193. Nikolich-Žugich J. 2018. The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol 19:10–19. https://doi.org/10.1038/s41590-017-0006-x
194. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. 2009. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis 200:172–180. https://doi.org/10.1086/599790
195. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. 2015. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine (Auckl) 33:4565–4571. https://doi.org/10.1016/j.vaccine.2015.07.003
196. Samson SI, Leventhal PS, Salamand C, Meng Y, Seet BT, Landolfi V, Greenberg D, Hollingsworth R. 2019. Immunogenicity of high-dose trivalent inactivated influenza vaccine: a systematic review and meta-analysis. Expert Rev Vaccines 18:295–308. https://doi.org/10.1080/14760584.2019.1575734
197. Pulendran B, S. Arunachalam P, O'Hagan DT. 2021. Emerging concepts in the science of vaccine adjuvants. Nat Rev Drug Discov 20:454–475. https://doi.org/10.1038/s41573-021-00163-y
198. Tregoning JS, Russell RF, Kinnear E. 2018. Adjuvanted influenza vaccines. Hum Vaccin Immunother 14:550–564. https://doi.org/10.1080/21645515.2017.1415684
199. O'Hagan DT, Ott GS, De Gregorio E, Seubert A. 2012. The mechanism of action of MF59 - an innately attractive adjuvant formulation. Vaccine (Auckl) 30:4341–4348. https://doi.org/10.1016/j.vaccine.2011.09.061
200. Papi A, Ison MG, Langley JM, Lee D-G, Leroux-Roels I, Martinon-Torres F, Schwarz TF, van Zyl-Smit RN, Campora L, Dezutter N, de Schrevel N, Fissette L, David M-P, Van der Wielen M, Kostanyan L, Hulstrøm V, AReSVi-006 Study Group. 2023. Respiratory syncytial virus prefusion F protein vaccine in older adults. N Engl J Med 388:595–608. https://doi.org/10.1056/NEJMoa2209604
201. Song JY, Choi WS, Heo JY, Kim EJ, Lee JS, Jung DS, Kim S-W, Park K-H, Eom JS, Jeong SJ, et al. 2023. Immunogenicity and safety of SARS-CoV-2 recombinant protein nanoparticle vaccine GBP510 adjuvanted with AS03: interim results of a randomised, active-controlled, observer-blinded, phase 3 trial. eClinMed 64:102140. https://doi.org/10.1016/j.eclinm.2023.102140
202. Batista-Duharte A, Martínez DT, Carlos IZ. 2018. Efficacy and safety of immunological adjuvants. Where is the cut-off? Biomed Pharmacother 105:616–624. https://doi.org/10.1016/j.biopha.2018.06.026
203. Chan W, Zhou H, Kemble G, Jin H. 2008. The cold adapted and temperature sensitive influenza A/Ann Arbor/6/60 virus, the master donor virus for live attenuated influenza vaccines, has multiple defects in replication at the restrictive temperature. Virology (Auckl) 380:304–311. https://doi.org/10.1016/j.virol.2008.07.027
204. Maassab HF. 1967. Adaptation and growth characteristics of influenza virus at 25 degrees c. Nature 213:612–614. https://doi.org/10.1038/213612a0
205. Lindsey BB, Jagne YJ, Armitage EP, Singanayagam A, Sallah HJ, Drammeh S, Senghore E, Mohammed NI, Jeffries D, Höschler K, Tregoning JS, Meijer A, Clarke E, Dong T, Barclay W, Kampmann B, de Silva TI. 2019. Effect of a Russian-backbone live-attenuated influenza vaccine with an updated pandemic H1N1 strain on shedding and immunogenicity among children in The Gambia: an open-label, observational, phase 4 study. Lancet Respir Med 7:665–676. https://doi.org/10.1016/S2213-2600(19)30086-4
206. Thwaites RS, Uruchurtu ASS, Negri VA, Cole ME, Singh N, Poshai N, Jackson D, Hoschler K, Baker T, Scott IC, Ros XR, Cohen ES, Zambon M, Pollock KM, Hansel TT, Openshaw PJM. 2023. Early mucosal events promote distinct mucosal and systemic antibody responses to live attenuated influenza vaccine. Nat Commun 14:8053. https://doi.org/10.1038/s41467-023-43842-7
207. Hoft DF, Babusis E, Worku S, Spencer CT, Lottenbach K, Truscott SM, Abate G, Sakala IG, Edwards KM, Creech CB, Gerber MA, Bernstein DI, Newman F, Graham I, Anderson EL, Belshe RB. 2011. Live and inactivated influenza vaccines induce similar humoral responses, but only live vaccines induce diverse T-cell responses in young children. J Infect Dis 204:845–853. https://doi.org/10.1093/infdis/jir436
208. Mohn KG-I, Bredholt G, Brokstad KA, Pathirana RD, Aarstad HJ, Tøndel C, Cox RJ. 2015. Longevity of B-cell and T-cell responses after live attenuated influenza vaccination in children. J Infect Dis 211:1541–1549. https://doi.org/10.1093/infdis/jiu654
209. He XS, Holmes TH, Zhang C, Mahmood K, Kemble GW, Lewis DB, Dekker CL, Greenberg HB, Arvin AM. 2006. Cellular immune responses in

children and adults receiving inactivated or live attenuated influenza vaccines. J Virol 80:11756–11766. https://doi.org/10.1128/JVI.01460-06
210. Subbramanian RA, Basha S, Shata MT, Brady RC, Bernstein DI. 2010. Pandemic and seasonal H1N1 influenza hemagglutinin-specific T cell responses elicited by seasonal influenza vaccination. Vaccine (Auckl) 28:8258–8267. https://doi.org/10.1016/j.vaccine.2010.10.077
211. Sridhar S, Brokstad KA, Cox RJ. 2015. Influenza vaccination strategies: comparing inactivated and live attenuated influenza vaccines. Vaccines (Basel) 3:373–389. https://doi.org/10.3390/vaccines3020373
212. Ilyushina NA, Haynes BC, Hoen AG, Khalenkov AM, Housman ML, Brown EP, Ackerman ME, Treanor JJ, Luke CJ, Subbarao K, Wright PF. 2015. Live attenuated and inactivated influenza vaccines in children. J Infect Dis 211:352–360. https://doi.org/10.1093/infdis/jiu458
213. Mohn KG-I, Brokstad KA, Pathirana RD, Bredholt G, Jul-Larsen Å, Trieu MC, Lartey SL, Montemoli E, Tøndel C, Aarstad HJ, Cox RJ. 2016. Live attenuated influenza vaccine in children induces B-cell responses in tonsils. J Infect Dis 214:722–731. https://doi.org/10.1093/infdis/jiw230
214. Pebody RG, Sinnathamby MA, Warburton F, Andrews N, Boddington NL, Zhao H, Yonova I, Ellis J, Tessier E, Donati M, Elliot AJ, Hughes HE, Pathirannehelage S, Byford R, Smith GE, de Lusignan S, Zambon M. 2018. Uptake and impact of vaccinating primary school-age children against influenza: experiences of a live attenuated influenza vaccine programme, England, 2015/16. Euro Surveill 23:1700496. https://doi.org/10.2807/1560-7917.ES.2018.23.25.1700496
215. Islam S, Mohn KG-I, Krammer F, Sanne M, Bredholt G, Jul-Larsen Å, Tete SM, Zhou F, Brokstad KA, Cox RJ. 2017. Influenza A haemagglutinin specific IgG responses in children and adults after seasonal trivalent live attenuated influenza vaccination. Vaccine (Auckl) 35:5666–5673. https://doi.org/10.1016/j.vaccine.2017.08.044
216. Islam S, Zhou F, Lartey S, Mohn KGI, Krammer F, Cox RJ, Brokstad KA. 2019. Functional immune response to influenza H1N1 in children and adults after live attenuated influenza virus vaccination. Scand J Immunol 90:e12801. https://doi.org/10.1111/sji.12801
217. Audsley JM, Tannock GA. 2008. Cell-based influenza vaccines: progress to date. Drugs (Abingdon Engl) 68:1483–1491. https://doi.org/10.2165/00003495-200868110-00002
218. Cox MMJ, Hashimoto Y. 2011. A fast track influenza virus vaccine produced in insect cells. J Invertebr Pathol 107:S31–41. https://doi.org/10.1016/j.jip.2011.05.003
219. Seqirus UK Limited. Cell-based quadrivalent influenza vaccine (Surface Antigen, Inactivated) seqirus suspension for injection in pre-filled syringe. Available from: https://www.medicines.org.uk/emc/product/12882/smpc. Retrieved 8 Aug 2024.
220. Barr IG, Donis RO, Katz JM, McCauley JW, Odagiri T, Trusheim H, Tsai TF, Wentworth DE. 2018. Cell culture-derived influenza vaccines in the severe 2017-2018 epidemic season: a step towards improved influenza vaccine effectiveness. NPJ Vaccines 3:44. https://doi.org/10.1038/s41541-018-0079-z
221. Centers for Disease Control and Prevention (CDC). How influenza (flu) vaccines are made. Available from: https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm#recombinant. Retrieved 8 Aug 2024.
222. Centers for Disease Control and Prevention. Cell-based flu vaccines. Available from: https://www.cdc.gov/flu/prevent/cell-based.htm. Retrieved 8 Aug 2024.
223. Rajaram S, Boikos C, Gelone DK, Gandhi A. 2020. Influenza vaccines: the potential benefits of cell-culture isolation and manufacturing. Ther Adv Vaccines Immunother 8:2515135520908121. https://doi.org/10.1177/2515135520908121
224. Subbarao K, Barr I. 2019. A tale of two mutations: beginning to understand the problems with egg-based influenza vaccines? Cell Host Microbe 25:773–775. https://doi.org/10.1016/j.chom.2019.05.012
225. Peck H, Laurie KL, Rockman S, Leung V, Lau H, Soppe S, Rynehart C, Baas C, Trusheim H, Barr IG. 2021. Enhanced isolation of influenza viruses in qualified cells improves the probability of well-matched vaccines. NPJ Vaccines 6:149. https://doi.org/10.1038/s41541-021-00415-3
226. Matsumoto S, Chong Y, Kang D, Ikematsu H. 2019. High genetic stability in MDCK-SIAT1 passaged human influenza viruses. J Infect Chemother 25:222–224. https://doi.org/10.1016/j.jiac.2018.08.012
227. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, Cox MMJ, PSC12 Study Team. 2017. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. N Engl J Med 376:2427–2436. https://doi.org/10.1056/NEJMoa1608862
228. Arunachalam AB, Post P, Rudin D. 2021. Unique features of a recombinant haemagglutinin influenza vaccine that influence vaccine performance. NPJ Vaccines 6:144. https://doi.org/10.1038/s41541-021-00403-7
229. Felberbaum RS. 2015. The baculovirus expression vector system: a commercial manufacturing platform for viral vaccines and gene therapy vectors. Biotechnol J 10:702–714. https://doi.org/10.1002/biot.201400438
230. Treanor JJ, El Sahly H, King J, Graham I, Izikson R, Kohberger R, Patriarca P, Cox M. 2011. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok) against influenza in healthy adults: a randomized, placebo-controlled trial. Vaccine (Auckl) 29:7733–7739. https://doi.org/10.1016/j.vaccine.2011.07.128
231. Franconeri L, Antona D, Cauchemez S, Lévy-Bruhl D, Paireau J. 2023. Two-dose measles vaccine effectiveness remains high over time: a French observational study, 2017-2019. Vaccine (Auckl) 41:5797–5804. https://doi.org/10.1016/j.vaccine.2023.08.018
232. Helena De Oliveira L, Jauregui B, Carvalho AF, Giglio N. 2017. Impact and effectiveness of meningococcal vaccines: a review. Rev Panam Salud Publica 41:e158. https://doi.org/10.26633/RPSP.2017.158
233. UK Health Security Agency. 2024. Surveillance of influenza and other seasonal respiratory viruses in the UK, winter 2023 to 2024. Available from: https://www.gov.uk/government/statistics/surveillance-of-influenza-and-other-seasonal-respiratory-viruses-in-the-uk-winter-2023-to-2024/surveillance-of-influenza-and-other-seasonal-respiratory-viruses-in-the-uk-winter-2023-to-2024#vaccination. Retrieved 8 Aug 2024.
234. Frutos AM, Price AM, Harker E, Reeves EL, Ahmad HM, Murugan V, Martin ET, House S, Saade EA, Zimmerman RK, et al. 2024. Interim estimates of 2023-24 seasonal influenza vaccine effectiveness - United States. MMWR Morb Mortal Wkly Rep 73:168–174. https://doi.org/10.15585/mmwr.mm7308a3
235. Gebre MS, Brito LA, Tostanoski LH, Edwards DK, Carfi A, Barouch DH. 2021. Novel approaches for vaccine development. Cell 184:1589–1603. https://doi.org/10.1016/j.cell.2021.02.030
236. Gary EN, Weiner DB. 2020. DNA vaccines: prime time is now. Curr Opin Immunol 65:21–27. https://doi.org/10.1016/j.coi.2020.01.006
237. Liu MA. 2003. DNA vaccines: a review. J Intern Med 253:402–410. https://doi.org/10.1046/j.1365-2796.2003.01140.x
238. Central Drugs Standard Control Organization. Corona virus 2019-nCoV vaccine (Recombinant) summary of product characteristics. Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadSmPC/6.%20ZyCoVD%203mg_Cadila_SmPC,%20Factsheet,%20PI.pdf. Retrieved 8 Aug 2024.
239. Mallapaty S. 2021. India's DNA COVID vaccine is a world first – more are coming. Nature 597:161–162. https://doi.org/10.1038/d41586-021-02385-x
240. Shafaati M, Saidijam M, Soleimani M, Hazrati F, Mirzaei R, Amirheidari B, Tanzadehpanah H, Karampoor S, Kazemi S, Yavari B, Mahaki H, Safaei M, Rahbarizadeh F, Samadi P, Ahmadyousefi Y. 2021. A brief review on DNA vaccines in the era of COVID-19. Fut Virol. https://doi.org/10.2217/fvl-2021-0170
241. Pardi N, Hogan MJ, Porter FW, Weissman D. 2018. mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov 17:261–279. https://doi.org/10.1038/nrd.2017.243
242. Ma N, Xia Z-W, Zhang Z-G, Nian X-X, Li X-D, Gong Z, Zhang G-M, Le Y, Zhou R, Zhang J-Y, Yang X-M. 2023. Development of an mRNA vaccine against a panel of heterologous H1N1 seasonal influenza viruses using a consensus hemagglutinin sequence. Emerg Microb Infect 12:2202278. https://doi.org/10.1080/22221751.2023.2202278
243. Gunter HM, Idrisoglu S, Singh S, Han DJ, Ariens E, Peters JR, Wong T, Cheetham SW, Xu J, Rai SK, Feldman R, Herbert A, Marcellin E, Tropee R, Munro T, Mercer TR. 2023. mRNA vaccine quality analysis using RNA sequencing. Nat Commun 14:5663. https://doi.org/10.1038/s41467-023-41354-y
244. Gote V, Bolla PK, Kommineni N, Butreddy A, Nukala PK, Palakurthi SS, Khan W. 2023. A comprehensive review of mRNA vaccines. Int J Mol Sci 24:2700. https://doi.org/10.3390/ijms24032700
245. Pardi N, Carreño JM, O'Dell G, Tan J, Bajusz C, Muramatsu H, Rijnink W, Strohmeier S, Loganathan M, Bielak D, Sung MMH, Tam YK, Krammer F, McMahon M. 2022. Development of a pentavalent broadly protective nucleoside-modified mRNA vaccine against influenza B viruses. Nat Commun 13:4677. https://doi.org/10.1038/s41467-022-32149-8

246. Karikó K, Buckstein M, Ni H, Weissman D. 2005. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity 23:165–175. https://doi.org/10.1016/j.immuni.2005.06.008
247. Wang Z, Jacobus EJ, Stirling DC, Krumm S, Flight KE, Cunliffe RF, Mottl J, Singh C, Mosscrop LG, Santiago LA, Vogel AB, Kariko K, Sahin U, Erbar S, Tregoning JS. 2023. Reducing cell intrinsic immunity to mRNA vaccine alters adaptive immune responses in mice. Mol Ther Nucleic Acids 34:102045. https://doi.org/10.1016/j.omtn.2023.102045
248. Whitaker JA, Sahly HME, Healy CM. 2023. mRNA vaccines against respiratory viruses. Curr Opin Infect Dis 36:385–393. https://doi.org/10.1097/QCO.0000000000000948
249. Rzymski P, Szuster-Ciesielska A, Dzieciątkowski T, Gwenzi W, Fal A. 2023. mRNA vaccines: the future of prevention of viral infections? J Med Virol 95:e28572. https://doi.org/10.1002/jmv.28572
250. Lee S, Ryu JH. 2021. Influenza viruses: innate immunity and mRNA vaccines. Front Immunol 12:710647. https://doi.org/10.3389/fimmu.2021.710647
251. Langer J, Welch VL, Moran MM, Cane A, Lopez SMC, Srivastava A, Enstone AL, Sears A, Markus KJ, Heuser M, Kewley RM, Whittle IJ. 2023. High clinical burden of influenza disease in adults aged ≥ 65 years: can we do better? a systematic literature review. Adv Ther 40:1601–1627. https://doi.org/10.1007/s12325-023-02432-1
252. Carter C, Houser KV, Yamshchikov GV, Bellamy AR, May J, Enama ME, Sarwar U, Larkin B, Bailer RT, Koup R, Chen GL, Patel SM, Winokur P, Belshe R, Dekker CL, Graham BS, Ledgerwood JE, VRC 703 study team. 2019. Safety and immunogenicity of investigational seasonal influenza hemagglutinin DNA vaccine followed by trivalent inactivated vaccine administered intradermally or intramuscularly in healthy adults: an open-label randomized phase 1 clinical trial. PLoS ONE 14:e0222178. https://doi.org/10.1371/journal.pone.0222178
253. Crank MC, Gordon IJ, Yamshchikov GV, Sitar S, Hu Z, Enama ME, Holman LA, Bailer RT, Pearce MB, Koup RA, Mascola JR, Nabel GJ, Tumpey TM, Schwartz RM, Graham BS, Ledgerwood JE, VRC 308 Study Team. 2015. Phase 1 study of pandemic H1 DNA vaccine in healthy adults. PLoS ONE 10:e0123969. https://doi.org/10.1371/journal.pone.0123969
254. DeZure AD, Coates EE, Hu Z, Yamshchikov GV, Zephir KL, Enama ME, Plummer SH, Gordon IJ, Kaltovich F, Andrews S, McDermott A, Crank MC, Koup RA, Schwartz RM, Bailer RT, Sun X, Mascola JR, Tumpey TM, Graham BS, Ledgerwood JE. 2017. An avian influenza H7 DNA priming vaccine is safe and immunogenic in a randomized phase I clinical trial. NPJ Vaccines 2:15. https://doi.org/10.1038/s41541-017-0016-6
255. Houser KV, Yamshchikov GV, Bellamy AR, May J, Enama ME, Sarwar U, Larkin B, Bailer RT, Koup R, Paskel M, Subbarao K, Anderson E, Bernstein DI, Creech B, Keyserling H, Spearman P, Wright PF, Graham BS, Ledgerwood JE, VRC 702 study team. 2018. DNA vaccine priming for seasonal influenza vaccine in children and adolescents 6 to 17 years of age: a phase 1 randomized clinical trial. PLoS ONE 13:e0206837. https://doi.org/10.1371/journal.pone.0206837
256. Ledgerwood JE, Hu Z, Costner P, Yamshchikov G, Enama ME, Plummer S, Hendel CS, Holman L, Larkin B, Gordon I, Bailer RT, Poretz DM, Sarwar U, Kabadi A, Koup R, Mascola JR, Graham BS, VRC 307 and VRC 309 Study Teams. 2015. Phase I clinical evaluation of seasonal influenza hemagglutinin (HA) DNA vaccine prime followed by trivalent influenza inactivated vaccine (IIV3) boost. Contemp Clin Trials 44:112–118. https://doi.org/10.1016/j.cct.2015.08.006
257. Ledgerwood JE, Zephir K, Hu Z, Wei C-J, Chang L, Enama ME, Hendel CS, Sitar S, Bailer RT, Koup RA, Mascola JR, Nabel GJ, Graham BS, VRC 310 Study Team. 2013. Prime-boost interval matters: a randomized phase 1 study to identify the minimum interval necessary to observe the H5 DNA influenza vaccine priming effect. J Infect Dis 208:418–422. https://doi.org/10.1093/infdis/jit180
258. Ledgerwood JE, Wei C-J, Hu Z, Gordon IJ, Enama ME, Hendel CS, McTamney PM, Pearce MB, Yassine HM, Boyington JC, Bailer R, Tumpey TM, Koup RA, Mascola JR, Nabel GJ, Graham BS. 2011. DNA priming and influenza vaccine immunogenicity: two phase 1 open label randomised clinical trials. Lancet Infect Dis 11:916–924. https://doi.org/10.1016/S1473-3099(11)70240-7
259. ModernaTX Inc. A study of mRNA-1010 seasonal influenza vaccine in adults (NCT05415462). Accessed August 2024. https://www.clinicaltrials.gov/study/NCT05415462?term=NCT05415462&rank=1.
260. ModernaTX Inc. A study of mRNA-1010 seasonal influenza vaccine in adults 50 years old and older (NCT05566639). Available from: https://www.clinicaltrials.gov/study/NCT05566639?term=mRNA-1010&aggFilters=phase:3&rank=3. Retrieved 8 Aug 2024.
261. Sanofi Pasteur. Study to assess the safety and immunogenicity of monovalent mRNA NA vaccine in adult participants 18 years of age and older (NCT05426174). Available from: https://www.clinicaltrials.gov/study/NCT05426174?cond=influenza&intr=%20mRNA%20QIV&rank=4. Retrieved 8 Aug 2024.
262. Sanofi Pasteur. Safety and immunogenicity of quadrivalent influenza mRNA vaccine MRT5410 in adult participants 18 years of age and older (NCT05624606). Available from: https://www.clinicaltrials.gov/study/NCT05624606?cond=influenza&intr=%20mRNA%20QIV&rank=1. Retrieved 8 Aug 2024.
263. Sanofi Pasteur. Safety and immunogenicity of quadrivalent influenza mRNA vaccine MRT5413 in adult participants 18 years of age and older (NCT05650554). Available from: https://www.clinicaltrials.gov/study/NCT05650554?cond=influenza&intr=%20mRNA%20QIV&rank=2. Retrieved 8 Aug 2024.
264. Sanofi Pasteur. Safety and immunogenicity of quadrivalent influenza mRNA vaccine MRT5407 in adult participants18 years of age and older (NCT05553301). Available from: https://www.clinicaltrials.gov/study/NCT05553301?cond=influenza&intr=%20mRNA%20QIV&rank=3. Retrieved 8 Aug 2024.
265. National Institute of Allergy and Infectious Diseases (NIAID). A study to evaluate the safety and immunogenicity of two doses of DCVC H1 HA mRNA-LNP in healthy adults (NCT05945485). Available from: https://www.clinicaltrials.gov/study/NCT05945485?cond=influenza&intr=%20mRNA%20QIV&rank=8. Retrieved 8 Aug 2024.
266. National Institute of Allergy and Infectious Diseases (NIAID). A study to evaluate the safety and immunogenicity of a single dose of H1ssF-3928 mRNA-LNP in healthy adults (NCT05755620). Available from: https://www.clinicaltrials.gov/study/NCT05755620?cond=influenza&intr=%20mRNA%20QIV&rank=9. Retrieved 8 Aug 2024.
267. Seqirus. Safety, reactogenicity, and immunogenicity study of a self-amplifying mRNA influenza vaccine in healthy adults (NCT06028347). Available from: https://www.clinicaltrials.gov/study/NCT06028347?cond=influenza&intr=%20mRNA&rank=1. Retrieved 8 Aug 2024.
268. GlaxoSmithKline. A study to assess the safety and immune response of a vaccine against influenza in healthy younger and older adults (NCT05823974). Available from: https://www.clinicaltrials.gov/study/NCT05823974?cond=influenza&intr=%20mRNA&rank=7. Retrieved 8 Aug 2024. , 2024
269. GlaxoSmithKline. A study on the safety, reactogenicity and immune response of a vaccine against influenza in healthy younger and older adults (NCT05446740). Available from: https://www.clinicaltrials.gov/study/NCT05446740?cond=influenza&intr=%20mRNA&page=2&rank=16. Retrieved 8 Aug 2024.
270. CureVac. A study to evaluate the safety, reactogenicity and immunogenicity of vaccine CVSQIV in healthy adults (NCT05252338). Available from: https://www.clinicaltrials.gov/study/NCT05252338?cond=influenza&intr=%20mRNA&page=3&rank=27. Retrieved 8 Aug 2024.
271. Arcturus Therapeutics Inc. Safety and immunogenicity first-in-human dose-ranging study of self-amplifying RNA seasonal influenza vaccine in adults (NCT06125691). Available from: https://www.clinicaltrials.gov/study/NCT06125691?cond=influenza&intr=%20mRNA&page=3&rank=28. Retrieved 8 Aug 2024.
272. Ananworanich J, Lee IT, Ensz D, Carmona L, Schaefers K, Avanesov A, Stadlbauer D, Choi A, Pucci A, McGrath S, Kuo HH, Henry C, Chen R, Huang W, Nachbagauer R, Paris R. 2024. Safety and immunogenicity of mRNA-1010, an investigational seasonal influenza vaccine, in healthy adults: final results from a phase 1/2 randomized trial. J Infect Dis:jiae329. https://doi.org/10.1093/infdis/jiae329
273. Feldman RA, Fuhr R, Smolenov I, Mick Ribeiro A, Panther L, Watson M, Senn JJ, Smith M, Almarsson Ö., Pujar HS, Laska ME, Thompson J, Zaks T, Ciaramella G. 2019. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine (Auckl) 37:3326–3334. https://doi.org/10.1016/j.vaccine.2019.04.074
274. Wang S, Liang B, Wang W, Li L, Feng N, Zhao Y, Wang T, Yan F, Yang S, Xia X. 2023. Viral vectored vaccines: design, development, preventive and therapeutic applications in human diseases. Signal Transduct Target Ther 8:149. https://doi.org/10.1038/s41392-023-01408-5
275. Travieso T, Li J, Mahesh S, Mello JDFRE, Blasi M. 2022. The use of viral vectors in vaccine development. NPJ Vaccines 7:75. https://doi.org/10.1038/s41541-022-00503-y

276. Heinz FX, Stiasny K. 2021. Distinguishing features of current COVID-19 vaccines: knowns and unknowns of antigen presentation and modes of action. NPJ Vaccines 6:104. https://doi.org/10.1038/s41541-021-00369-6
277. Van Kampen KR, Shi Z, Gao P, Zhang J, Foster KW, Chen D-T, Marks D, Elmets CA, Tang DC. 2005. Safety and immunogenicity of adenovirus-vectored nasal and epicutaneous influenza vaccines in humans. Vaccine (Auckl) 23:1029–1036. https://doi.org/10.1016/j.vaccine.2004.07.043
278. Zhan W, Muhuri M, Tai PWL, Gao G. 2021. Vectored immunotherapeutics for infectious diseases: can rAAVs be the game changers for fighting transmissible pathogens? Front Immunol 12:673699. https://doi.org/10.3389/fimmu.2021.673699
279. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, et al. 2021. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397:99–111. https://doi.org/10.1016/S0140-6736(20)32661-1
280. Buffin S, Peubez I, Barrière F, Nicolaï M-C, Tapia T, Dhir V, Forma E, Sève N, Legastelois I. 2019. Influenza A and B virus-like particles produced in mammalian cells are highly immunogenic and induce functional antibodies. Vaccine (Auckl) 37:6857–6867. https://doi.org/10.1016/j.vaccine.2019.09.057
281. Matsuda T, Tanijima T, Hirose A, Masumi-Koizumi K, Katsuda T, Yamaji H. 2020. Production of influenza virus-like particles using recombinant insect cells. Biochem Eng J 163:107757. https://doi.org/10.1016/j.bej.2020.107757
282. Ward BJ, Makarkov A, Séguin A, Pillet S, Trépanier S, Dhaliwall J, Libman MD, Vesikari T, Landry N. 2020. Efficacy, immunogenicity, and safety of a plant-derived, quadrivalent, virus-like particle influenza vaccine in adults (18-64 years) and older adults (>/=65 years): two multicentre, randomised phase 3 trials. Lancet 396:1491–1503. https://doi.org/10.1016/S0140-6736(20)32014-6
283. Pushko P, Tretyakova I. 2020. Influenza virus like particles (VLPs): opportunities for H7N9 vaccine development. Viruses 12:518. https://doi.org/10.3390/v12050518
284. Atsmon J, Kate-Ilovitz E, Shaikevich D, Singer Y, Volokhov I, Haim KY, Ben-Yedidia T. 2012. Safety and immunogenicity of multimeric-001--a novel universal influenza vaccine. J Clin Immunol 32:595–603. https://doi.org/10.1007/s10875-011-9632-5
285. Atmar RL, Bernstein DI, Winokur P, Frey SE, Angelo LS, Bryant C, Ben-Yedidia T, Roberts PC, El Sahly HM, Keitel WA. 2023. Safety and immunogenicity of Multimeric-001 (M-001) followed by seasonal quadrivalent inactivated influenza vaccine in young adults – a randomized clinical trial. Vaccine (Auckl) 41:2716–2722. https://doi.org/10.1016/j.vaccine.2023.03.023
286. Kurosky SK, Davis KL, Krishnarajah G. 2017. Effect of combination vaccines on completion and compliance of childhood vaccinations in the United States. Hum Vaccin Immunother 13:2494–2502. https://doi.org/10.1080/21645515.2017.1362515
287. ClinicalTrials.gov. A study to evaluate the safety, tolerability, and immunogenicity of combined modified RNA vaccine candidates against COVID-19 and influenza. ClinicalTrials.gov Identifier: NCT05596734. Available from: https://clinicaltrials.gov/study/NCT05596734. Retrieved 8 Aug 2024.
288. ClinicalTrials.gov. A Study of mRNA-based influenza and SARS-CoV-2 (COVID-19) multi-component vaccines in healthy adults. ClinicalTrials.gov identifier: NCT05827926. Retrieved 8 Aug 2024. https://clinicaltrials.gov/study/NCT05827926.
289. Kreier F. 2024. Combined COVID-flu vaccines are coming: Moderna jab clears major test. Nat New Biol. https://doi.org/10.1038/d41586-024-02121-1
290. ClinicalTrials.gov. A study of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in healthy adult participants, ≥50 years of age. Retrieved 12 Aug 2024. https://clinicaltrials.gov/study/NCT06097273.
291. Westgeest KB, Russell CA, Lin X, Spronken MIJ, Bestebroer TM, Bahl J, van Beek R, Skepner E, Halpin RA, de Jong JC, Rimmelzwaan GF, Osterhaus A, Smith DJ, Wentworth DE, Fouchier RAM, de Graaf M. 2014. Genomewide analysis of reassortment and evolution of human influenza A(H3N2) viruses circulating between 1968 and 2011. J Virol 88:2844–2857. https://doi.org/10.1128/JVI.02163-13
292. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, Tashkandi M, Bauch CT, Loeb M. 2013. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med 11:153. https://doi.org/10.1186/1741-7015-11-153
293. World Health Organisation. Global influenza programme. Available from: https://www.who.int/teams/global-influenza-programme/vaccines. Retrieved 8 Aug 2024.
294. Xie H, Wan XF, Ye Z, Plant EP, Zhao Y, Xu Y, Li X, Finch C, Zhao N, Kawano T, Zoueva O, Chiang MJ, Jing X, Lin Z, Zhang A, Zhu Y. 2015. H3N2 mismatch of 2014-15 northern hemisphere influenza vaccines and head-to-head comparison between human and ferret antisera derived antigenic maps. Sci Rep 5:15279. https://doi.org/10.1038/srep15279
295. McMillan CLD, Young PR, Watterson D, Chappell KJ. 2021. The next generation of influenza vaccines: towards a universal solution. Vaccines (Basel) 9:26. https://doi.org/10.3390/vaccines9010026
296. Hu L, Lao G, Liu R, Feng J, Long F, Peng T. 2023. The race toward a universal influenza vaccine: front runners and the future directions. Antiviral Res 210:105505. https://doi.org/10.1016/j.antiviral.2022.105505
297. Folschweiller N, Vanden Abeele C, Chu L, Van Damme P, García-Sastre A, Krammer F, Nachbagauer R, Palese P, Solórzano A, Bi D, David M-P, Friel D, Innis BL, Koch J, Mallett CP, Rouxel RN, Salaun B, Vantomme V, Verheust C, Struyf F. 2022. Reactogenicity, safety, and immunogenicity of chimeric haemagglutinin influenza split-virion vaccines, adjuvanted with AS01 or AS03 or non-adjuvanted: a phase 1-2 randomised controlled trial. Lancet Infect Dis 22:1062–1075. https://doi.org/10.1016/S1473-3099(22)00024-X
298. Nachbagauer R, Feser J, Naficy A, Bernstein DI, Guptill J, Walter EB, Berlanda-Scorza F, Stadlbauer D, Wilson PC, Aydillo T, et al. 2021. A chimeric hemagglutinin-based universal influenza virus vaccine approach induces broad and long-lasting immunity in A randomized, placebo-controlled phase I trial. Nat Med 27:106–114. https://doi.org/10.1038/s41591-020-1118-7
299. Pulendran B. 2024. Integrated organ immunity: a path to a universal vaccine. Nat Rev Immunol 24:81–82. https://doi.org/10.1038/s41577-024-00990-1
300. Hodgson D, Baguelin M, van Leeuwen E, Panovska-Griffiths J, Ramsay M, Pebody R, Atkins KE. 2017. Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis. Lancet Public Health 2:e74–e81. https://doi.org/10.1016/S2468-2667(16)30044-5
301. Regan AK, Arriola CS, Couto P, Duca L, Loayza S, Nogareda F, de Almeida WAF, Antman J, Araya S, Avendaño Vigueras MA, et al. 2023. Severity of influenza illness by seasonal influenza vaccination status among hospitalised patients in four South American countries, 2013-19: a surveillance-based cohort study. Lancet Infect Dis 23:222–232. https://doi.org/10.1016/S1473-3099(22)00493-5

AUTHOR BIOS

Tristan W. Clark is a Professor and Honorary Consultant in Infectious Diseases at the University of Southampton and University Hospitals Southampton NHS Trust. His research involves clinical trials of vaccines, antivirals and rapid diagnostic tests for influenza and other infections. He has been awarded grant funding from NIHR, Research Councils, EU, and Industry and has published results of his trials in The New England Journal of Medicine and Lancet series journals. During the COVID-19 pandemic he has acted as an advisor to the UK Department of Health and Social Care on diagnostic testing.

John S. Tregoning is Professor of Vaccine Immunology at Imperial College London, UK. He has worked on vaccines for over 20 years. His team works on the preclinical mechanisms of vaccine-induced protection, with a focus on respiratory viral infections including RSV and influenza.

Helen Lister trained as a children's nurse and worked in community and hospital settings before embarking on a research career. She received NIHR fellowships to undertake an MSc and subsequent PhD in healthcare research and worked in clinical and academic research investigating childhood food allergy. She subsequently moved to the pharmaceutical industry where she is a Medical Advisor in the field of vaccines and public health.

Tiziano Poletti has been Medical Advisor at Sanofi Vaccines UK for the past 2 years and has worked in medical and regulatory affairs in the pharmaceutical industry for over 8 years. He previously worked in research in the field of biomaterials investigating monocyte/macrophage-mediated inflammatory responses to different foreign materials using primary cell lines.

Femy Amin is a pharmacist by background with a clinical MSc degree, specialising in mental health and psychopharmacology. Her professional journey encompasses clinical practice, teaching, research and roles within the pharmaceutical industry. As a Medical Affairs Lead in the pharmaceutical sector, her expertise lies in Women's Health and Vaccines.

Professor **Jonathan S. Nguyen-Van-Tam**, Kt, MBE, FMedSci, is a doctor and public health specialist with a clinical background in emergency medicine, anaesthesia and infectious diseases. He is an expert on respiratory viruses and pandemics and currently Senior Strategy Adviser to the University of Nottingham School of Medicine. His career has also taken him to Public Health England, the World Health Organization, and the pharmaceutical and vaccine industries. He has published well over 200 peer-reviewed scientific papers. Jonathan was seconded to the Department of Health and Social Care in 2017-22 as Deputy Chief Medical Officer. He is well-known for his leadership role during the COVID-19 pandemic, particularly the acquisition and rollout of vaccines and antiviral drugs in the UK. He received a knighthood from Her late Majesty the Queen in her 2022 New Year's Honours List, for services to public health.