19

Influenza

The disease

Influenza is an acute viral infection of the respiratory tract. There are 3 types of influenza virus: A, B and C. Influenza A and influenza B are responsible for most clinical illness. Influenza is highly infectious with a usual incubation period of 1 to 3 days.

The disease is characterised by the sudden onset of fever, chills, headache, myalgia and extreme fatigue. Other common symptoms include a dry cough, sore throat and stuffy nose. For otherwise healthy individuals, influenza is an unpleasant but usually self-limiting disease with recovery usually within 2 to 7 days. The illness may be complicated by (and may present as) bronchitis, secondary bacterial pneumonia or, in children, otitis media. Influenza can be complicated more unusually by meningitis, encephalitis or meningoencephalitis. The risk of serious illness from influenza is higher amongst children under 6 months of age (Poehling *et al*., 2006; Ampofo *et al*., 2006; Coffin *et al*., 2007; Zhou *et al*, 2012), older people (Thompson *et al*., 2003 and 2004; Zhou *et al*, 2012), those with underlying health conditions such as respiratory or cardiac disease, chronic neurological conditions, and immunosuppression and also in pregnant women (Neuzil *et al*., 1998; O'Brien *et al*., 2004; Nicoll *et al*., 2008 and Pebody *et al*., 2010). Influenza during pregnancy may also be associated with perinatal mortality, prematurity, smaller neonatal size and lower birth weight (Pierce *et al*., 2011; Mendez-Figueroa *et al*., 2011) and admission to intensive care (Vousden *et al*., 2021). Although primary influenza pneumonia is a rare complication that may occur at any age and carries a high case fatality rate (Barker and Mullooly, 1982), it was seen more frequently during the 2009 pandemic and the following influenza season. Serological studies in healthcare professionals have shown that approximately 30 to 50% of influenza infections can be asymptomatic (Wilde *et al*., 1999) but the proportion of influenza infections that are asymptomatic may vary depending on the characteristics of the influenza strain.

Transmission is by droplets, aerosol, or through direct contact with respiratory secretions of someone with the infection (Killingley and Nguyen-Van-Tam 2013). Influenza spreads rapidly, especially in closed communities such as nursing and residential homes and schools. Most cases in the UK tend to occur during an 8- to 10-week period during the winter. The timing, extent and severity of this 'seasonal' influenza can all vary.

Influenza A viruses cause outbreaks most years and it is these viruses that are the usual cause of epidemics. Large epidemics occur intermittently. Influenza B tends to cause less severe disease and smaller outbreaks overall. The burden of influenza B disease is mostly in children when the severity of illness can be similar to that associated with influenza A.

Changes in the principal surface antigens of influenza A – haemagglutinin and neuraminidase – make these viruses antigenically labile. Minor changes, described as antigenic drift, occur progressively from season to season. Antigenic shift occurs

periodically, resulting in major changes and the emergence of a new subtype with a different haemagglutinin protein. Because immunity from the previous virus may not protect completely against the new subtype, the population may have little or no immunity, and this may therefore lead to widespread epidemics or even a pandemic. Influenza B viruses are also subject to antigenic drift but with less frequent changes.

Three influenza pandemics occurred in the last century (in 1918, 1957 and 1968). The first influenza pandemic of this century was declared by the World Health Organization (WHO) in June 2009. This was caused by an influenza A(H1N1)v virus. The influenza A(H1N1)v pandemic caused higher rates of illness in children and young adults and lower rates of illness in adults aged 60 years and older when compared with 'seasonal' influenza (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, 2010). For most individuals the disease was mild. Symptoms were similar to those of 'seasonal' influenza, although gastrointestinal symptoms (vomiting and diarrhoea) were more commonly reported than is usual for 'seasonal' influenza. During the pandemic, there were fewer than 500 laboratory confirmed deaths from influenza A(H1N1)v in the UK with an overall estimated case fatality ratio of 0.25 per 1,000 clinical cases (95% confidence limits 0.13 to 0.4 per 1,000 clinical cases) (Presanis, *et al*., 2011). The highest mortality rates were in those with chronic neurological disease, respiratory disease and immunosuppression (Pebody *et al*., 2010). Individuals with morbid obesity (BMI>40) were also found to be at higher risk of severe outcome (both hospitalisation and death) following pandemic influenza infection compared to individuals with obesity and to normal weight individuals (Morgan *et al*.,2010; Fezeu *et al*.,2011; Van Kerkhove.,2011). Pregnant women were also at increased risk of complications (Jamison *et al*., 2009). Most of the serious complications arising from influenza A(H1N1) v infection occurred in people with underlying health conditions, but a significant proportion arose in people who had been previously healthy (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, 2010).

The influenza A(H1N1)v strain continued to cause widespread illness during the 2010 to 2011 influenza season and has continued to circulate seasonally (the virus is now known as A(H1N1)pdm09). Despite the recent emergence of the influenza A(H1N1)pdm09 strain, conditions still exist for the emergence of future influenza strains with potential to lead to another pandemic (for example, from influenza A H2, H5N1 or H7N9 strains).

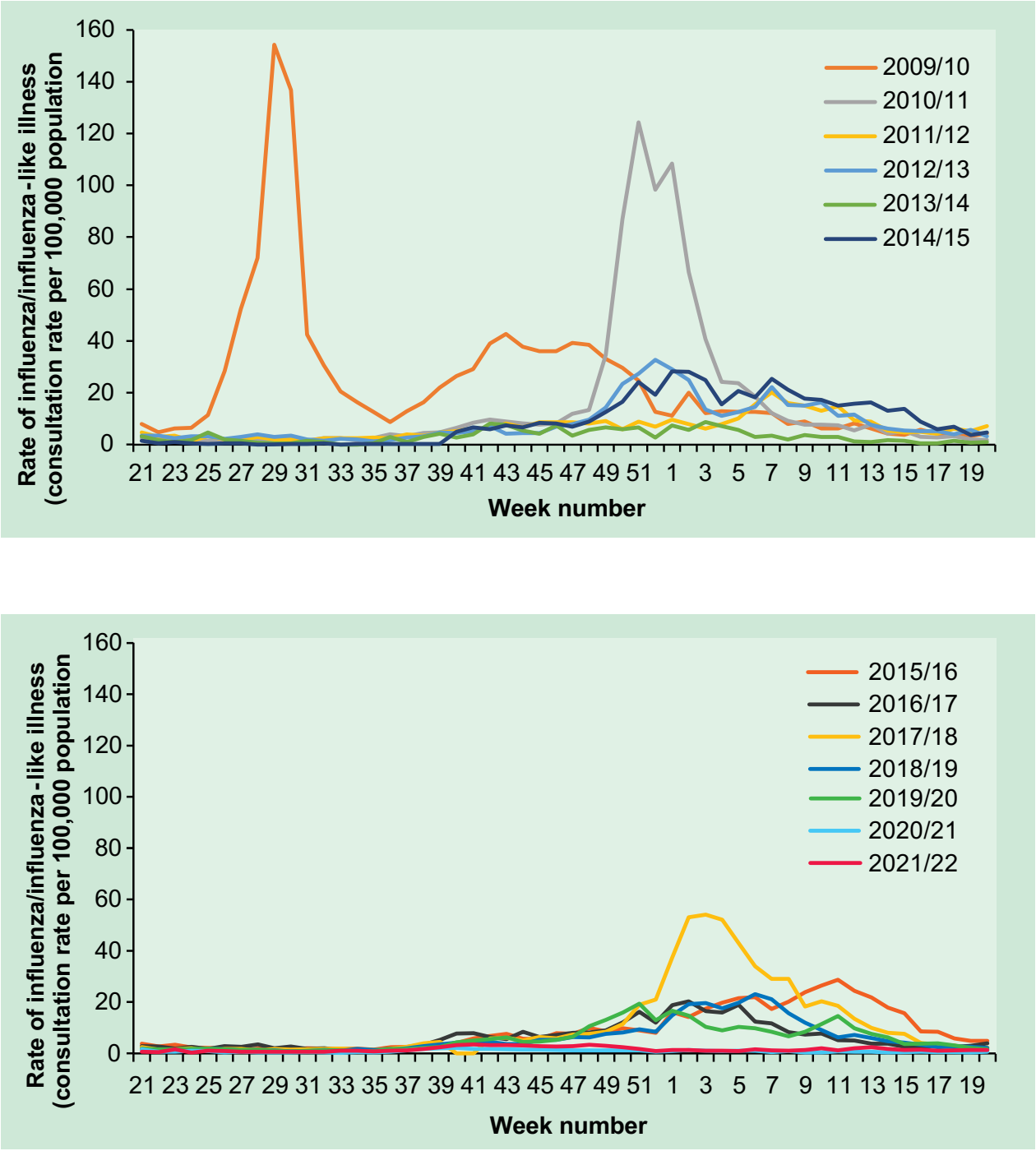

Figure 19.1 Rate of influenza/influenza-like illness episodes in England (weekly returns to Royal College of General Practitioners RCGP)), showing the variation in the timing and shape of influenza activity usually between weeks 37 and 15 (panel A 2009/11 to 2014/15, panel B 2015/16 to 2021/22, data separated for clarity). However, much of the influenza A(H1N1)v pandemic activity was outside that usual time window, demonstrated by the non-seasonal peak at week 29 in 2009/10. Data for 2009/10 may underestimate the extent of influenza-like illness due to the introduction of the National Pandemic Flu Service in England during 2009. Non-pharmaceutical interventions against COVID-19 were in place throughout 2020/21 and 2021/22 seasons. There may be differences in the epidemiology of influenza between the different countries in the UK. Data provided by UK Health Security Agency (UKHSA) (formerly Public Health England (PHE), formerly Health Protection Agency (HPA)) and RCGP.

History and epidemiology of the disease

Influenza activity is monitored in the UK through a variety of schemes based in primary and secondary care. One important indicator is based on reports of new consultations for influenza-like illness from sentinel GP practices, combined with virological surveillance.

Weekly reports are collated by the UK Health Security Agency (UKHSA) (formerly PHE). Additional information for England is provided by the Royal College of General Practitioners (RCGP), for Scotland by Public Health Scotland (formerly Health Protection Scotland), for Wales by Public Health Wales and for Northern Ireland by the Public Health Agency.

Official estimates of the number of deaths attributable to influenza are produced by UKHSA. These are inferred from the number of all-cause death registrations in the winter period that are above an expected seasonal level. However, as the cause of death is not examined directly, deaths above the expected level may include causes other than influenza such as cold weather-related conditions. Estimates of excess winter deaths potentially attributable to influenza in years in the last decade in England are published in the annual national flu reports and range from less than 1,000 (2005 to 2006, 2006 to 2007 and 2008 to 2009) to greater than 20,000 (2014 to 2015 and 2017 to 2018).

UKHSA also collects data on admissions to intensive care units and on deaths with a laboratory-confirmed influenza infection. Whilst it is not possible to ascertain all fatal cases where influenza was involved, investigation of such cases allows assessment of the characteristics of people most severely affected by influenza, including age and the responsible influenza type. An analysis by PHE, (now UKHSA) of data from fatal cases collected in England during the 2010 to 2011 influenza season, when influenza A(H1N1) pdm09 was the predominant circulating strain, gives an indication of the increased risk of death from influenza complications for those in clinical risk groups (see Table 19.1).

Table 19.1 Influenza-related population mortality rates and relative risk of death among those aged 6 months to under 65 years by clinical risk group in England, September 2010 to May 2011.

	Number of fatal flu cases (%)	Mortality rate per 100,000 population	Age-adjusted relative risk*
In a risk group	213 (59.8)	4.0	11.3 (9.1-14.0)
Not in any risk group	143 (40.2)	0.4	Baseline
Chronic renal disease	19 (5.3)	4.8	18.5 (11.5–29.7)
Chronic heart disease	32 (9.0)	3.7	10.7 (7.3-15.7)
Chronic respiratory disease	59 (16.6)	2.4	7.4 (5.5-10.0)
Chronic liver disease	32 (9.0)	15.8	48.2 (32.8-70.6)
Diabetes	26 (7.3)	2.2	5.8 (3.8-8.9)
Immunosuppression	71 (19.9)	20.0	47.3 (35.5-63.1)
Chronic neurological disease (excluding stroke/transient ischaemic attack)	42 (11.8)	14.7	40.4 (28.7-56.8)
Total (including 22 cases with no information on clinical risk factors)	378	0.8	

* Mantel-Haenszel age-adjusted rate ratio (RR), with corresponding exact 95% CI were calculated for each risk group using the 2 available age groups (from 6 months up to 15 years and from 16 to 64 years).

Table reproduced from the HPA *Surveillance of influenza and other respiratory viruses in the UK 2010 to 2011 report*

Influenza immunisation programme

Influenza immunisation has been recommended in the UK since the late 1960s, with the aim of directly protecting those in clinical risk groups who are at a higher risk of influenza associated morbidity and mortality. In 2000, the policy was extended to include all people aged 65 years or over (see later for age definition). The list of conditions that constitute a clinical risk group where influenza vaccine is indicated are reviewed regularly by the Joint Committee on Vaccination and Immunisation (JCVI). In 2010, pregnancy was added as a clinical risk category, and in October 2014 the JCVI advised that morbid obesity (defined as BMI 40+) should be considered a risk factor for seasonal influenza vaccination.

Uptake of influenza vaccination in those aged 65 years or over and in those aged under 65 years in a clinical risk group (excluding data on pregnant women) in the UK is shown in Table 19.2.

Table 19.2 Influenza vaccine uptake in the UK for people aged 65 years or over and, in brackets, aged under 65 years in a clinical risk group (excluding pregnant women). End of influenza vaccination campaign estimates.

Year	England (%)	Scotland (%)	Wales (%)	Northern Ireland (%)
2000/01	65.4	65	39	68
2001/02	67.5	65	59	72
2002/03	68.6	69	54	72.1 (55.8)
2003/04	71.0	72.5	63	73.4 (63.8)
2004/05	71.5 (39.9)	71.7 (39.3)	63	72.7 (65.2)
2005/06	75.3 (48.0)	77.8 (46.3)	68	76.8 (80.9)
2006/07	73.9 (42.1)	75.2 (37.8)	*	75.1 (71.2)
2007/08	73.5 (45.3)	74.3 (44.4)	64	75.7 (68.3)
2008/09	74.1 (47.1)	76.3 (47.8)	60 (41)	76.8 (74.0)
2009/10	72.4 (51.6)	75.0 (53.4)	64 (49)	77.0 (80.0)
2010/11	72.8 (50.4)	75.3 (56.1)	65.8 (48.6)	74.9 (78.7)
2011/12	74.0 (51.6)	76.6 (59.7)	67.7 (50.0)	77.0 (81.7)
2012/13	73.4 (51.3)	77.4 (59.2)	67.7 (49.7)	75.0 (80.2)
2013/14	73.2 (52.3)	77% (60.5)	68.3 (51.1)	75.4 (76.4)
2014/15	72.7 (50.3)	76.3 (54.0)	68.1 (49.3)	73.4 (71.8)
2015/16	71.0 (45.1)	74.5 (48.0)	66.6 (46.8)	74.4 (59.9)
2016/17	70.5 (48.6)	72.8 (44.9)	66.7 (46.9)	71.9 (57.1)
2017/18	72.9 (49.7)	73.7 (44.8)	68.8 (47.1)	71.8 (56.0)
2018/19	72.0 (48.0)	73.7 (42.4)	68.3 (47.1)	70.0 (52.4)
2019/20	72.4 (44.9)	74.0 (42.3)	69.4 (44.1)	74.8 (58.9)
2020/21	80.9 (53.0)	79.6 (55.9)	76.5 (51.0)	79.1 (67.8)
2021/22	82.3 (52.9)	90.2 (62.4)	78.0 (48.2)	54.5 (*)

* Data not available

The uptake of influenza vaccine by pregnant women is difficult to estimate as it is more challenging to determine a denominator accurately. The available data are shown in Table 19.3 but may underestimate uptake.

Table 19.3 Influenza vaccine uptake in the UK since the start of the influenza immunisation programme for pregnant women. End of influenza vaccination campaign estimates.

Year	England (%)	Scotland (%)	Wales (%)	Northern Ireland (%)
2010/11	38.0	65.6*	39.6	N/A
2011/12	27.4	41.1	31.7	58.4
2012/13	40.3	54.0	61.6	64.6
2013/14	39.8	49.2	43.8	58.0
2014/15	44.1	50.9	45.3	56.1
2015/16	42.3	51.2	47.8	55.1
2016/17	44.9	50.3	45.7	58.6
2017/18	47.2	49.4	72.7**	56.7
2018/19	45.2	44.5	74.2**	44.3
2019/20	43.7	42.9	78.5**	46.3
2020/21	43.6	53.3	81.5**	50.0
2021/22	37.9	55.2	78.5**	45.9

*Denominator incomplete

** Vaccine coverage in pregnant women was measured using a survey of pregnant women giving birth during January.

Information on vaccine uptake for the childhood programme and more detailed analyses of influenza vaccine uptake by individual clinical risk groups and by different age groups are made available by the UK public health bodies on their webpages.

Extension of the influenza programme to children

In 2012, JCVI recommended that the programme should be extended to all children aged two to less than seventeen years old (JCVI, 2012). JCVI advised that the vaccine of choice for the extension to the programme should be the live attenuated intranasal influenza vaccine (LAIV), given the evidence of superior effectiveness in young children, particularly after a single dose, and the potential protection against drifted strains. The route of administration also makes LAIV an easier vaccine to administer and more acceptable to parents and children when compared to an injectable vaccine.

The phased introduction of the extension of the influenza programme to children began in 2013. Those cohorts eligible for the programme in each UK country will be updated each season in the annual flu letter for England and the respective Chief Medical Officer letters for the Devolved Administrations.

Annual influenza vaccination programme letters

England:
https://www.gov.uk/government/collections/annual-flu-programme

Northern Ireland:
https://www.publichealth.hscni.net/search/node?keys=influenza+programme

Scotland:
https://www.sehd.scot.nhs.uk/index.asp?name=&org=&keyword=seasonal+flu

Wales:
https://www.gov.wales/health-circulars

Influenza vaccines

Because of the changing nature of influenza viruses, the World Health Organization (WHO) monitors the epidemiology of influenza viruses throughout the world. Each year it makes recommendations about the strains to be included in vaccines for the forthcoming winter for the northern and southern hemispheres (https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations).

Influenza vaccines are prepared in line with the WHO recommendations. All the vaccines currently used in the UK programme are quadrivalent, containing 4 strains: 2 subtypes of influenza A and both circulating lineages of influenza B. Trivalent vaccines omit an influenza B virus.

Most influenza vaccines are prepared from viruses grown in embryonated hens' eggs. There are also approved influenza vaccines produced on cell lines, from virus grown in cells (cell-based vaccines) or recombinant vaccines that use haemagglutinin antigen produced in insect cells from DNA sequences.

Manufacture of influenza vaccines is complex and conducted to a tight schedule, constrained by the period between the announcement of the WHO recommendations and the opportunity to vaccinate before the influenza season. Manufacturers may not be able to respond to unexpected demands for vaccine at short notice.

If a new influenza A subtype were to emerge with epidemic or pandemic potential (as occurred in 2009 with influenza A(H1N1)v), it is unlikely that the influenza vaccine will be well matched to the emerging strain. In these circumstances, as occurred during the second wave of the 2009 pandemic, a monovalent vaccine against that strain may be developed and implemented.

All but one of the influenza vaccines available in the UK are inactivated and cannot cause clinical influenza in those that are vaccinated. One vaccine, the live attenuated influenza vaccine (LAIV), contains live viruses that have been attenuated (weakened) and adapted to cold so that they can only replicate at the lower temperatures found in the nasal passage. These live viruses cannot replicate efficiently elsewhere in the body but may cause mild coryzal symptoms. The inactivated vaccines are administered by intramuscular injection. LAIV is administered by nasal spray.

All authorised influenza vaccines need to meet safety, efficacy and quality standards set by the Commission on Human Medicines. Since 1 January 2021, EU pharmaceutical law has applied to the UK only in Northern Ireland. The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for granting Marketing Authorisations (MA) for new medicinal products in Great Britain. A list of the influenza vaccines available in the UK is published ahead of the influenza season on the annual flu programme pages (available at: https://www.gov.uk/government/collections/annual-flu-programme).

Mismatches between the components in the vaccine and circulating viruses do occur from time to time and explains much of the variation in estimates of vaccine effectiveness (Osterholm *et al*., 2012). When antigenic drift does occur, vaccination is still recommended as some degree of protection may be conferred against the drifted strain and the vaccine should still offer protection against the other strains in the vaccine. Historically, for the trivalent vaccines which contain an influenza B strain from a single lineage, mismatches between the vaccines and the circulating B strain have occurred frequently. However, with the exception of 2014 to 2015, in most recent years, the vaccines have closely matched the influenza A viruses circulating during the influenza season.

After immunisation, protective immune responses may be achieved within 14 days. Although influenza activity is not usually significant in the UK before the middle of November, the influenza season can start early (as it did in 2003 to 2004). Therefore, the ideal time for immunisation is between September and early November. Protection afforded by the vaccine is thought to last for at least one influenza season. However, as the level of protection provided in subsequent seasons is likely to be low and there may be changes to the circulating strains from one season to the next, annual revaccination is recommended and important.

Vaccine effectiveness

The effectiveness and cost-effectiveness of influenza vaccine depends upon the composition of the vaccine, the circulating strains, the type of vaccine and the age of the individual being vaccinated.

A meta-analysis, which included studies when the influenza virus strains in the trivalent egg-based inactivated vaccine were drifted or mismatched with those in circulation, suggested an overall effectiveness against confirmed disease of 59% (95% confidence interval 51-67) in adults aged 18 to 65 years (Osterholm *et al*., 2012).

The LAIV is thought to provide broader protection than inactivated vaccines, and therefore has potential to offer better protection against strains that have undergone antigenic drift compared to the original virus strains in the vaccine (Ambose *et al*., 2011; Hoft *et al* 2011; Subbramanian *et al* 2010). LAIV has been shown to provide a higher level of protection for children than trivalent inactivated influenza vaccine (Belshe *et al*., 2007); a meta-analysis suggested an efficacy against confirmed disease of 83% (95% confidence interval 69-91) (Osterholm *et al.,* 2012; Ashkenazi *et al*., 2006; Fleming *et al*., 2006).

In August 2016, the JCVI was asked to review data from the 2015 to 2016 season in the UK and other countries, in light of emerging evidence of low effectiveness of the LAIV reported by the Centers for Disease Control and Prevention (CDC) in the United States (US). In contrast to the US, the UK data from the 2015 to 2016 season demonstrated the overall effectiveness and impact of childhood influenza vaccination and a reduction in cases of influenza both in those vaccinated, and in the population more widely. The JCVI

continued to recommend the use of the children's nasal spray flu vaccine for preventing flu in children and strongly supports the continuation of this important public health programme in the UK (JCVI., August 2016). The more recent UK results have confirmed consistently good effectiveness for LAIV (Pebody *et al*., 2016, Pebody *et al*., 2017; Pebody *et al*., 2020c). In addition, in areas that piloted the full primary school programme, indirect protection to both older and younger age groups has been demonstrated. (Pebody *et al*., 2015, Pebody *et al*,, 2018a, Sinnathamby *et al*.,2021)

The use of quadrivalent influenza vaccines containing a B strain from each lineage is expected to improve the match of the vaccine and therefore offer wider protection against circulating influenza B viruses. Several studies indicate that quadrivalent vaccine is likely to be cost effective when compared with the trivalent vaccine (Meir *et al*., 2015., Thommes *et al*., 2015). Because influenza B is relatively more common in children, the vaccines centrally purchased for the childhood programme in recent years have been quadrivalent preparations. As the childhood programme will contribute to better control of influenza B overall by reducing transmission across the population, modelling work by PHE was conducted to understand the benefit of quadrivalent vaccine in adults once the childhood programme is fully established in children of primary school age (Thorrington *et al*., 2017). This model suggests that there are relatively small health benefits to be gained by the use of quadrivalent vaccines, compared with trivalent vaccines in the elderly, but that the benefit is more substantial in at-risk adults under 65 years of age, including pregnant women. Surveillance is ongoing for the B Yamagata lineage following marked reduction in detections due to non-pharmaceutical interventions against COVID-19 throughout 2020 to 2022; demonstration of extinction of the Yamagata lineage would be indication for a return to trivalent influenza vaccines.

There is considerable evidence that immune responses to vaccination decline substantially with age (Haralambieva *et al*., 2015). Antibody responses in the elderly are lower than in younger adults and this is likely to translate into a lower effectiveness for influenza vaccines when compared with younger adults (Goodwin *et al*., 2006; Lang *et al*., 2012). During the 2016 to 2017 UK influenza season, the effectiveness of vaccine against medically attended, laboratory confirmed influenza in primary care in the elderly could not be demonstrated (Pebody *et al*., 2017). PHE conducted an age stratified analysis of pooled primary care data from 2010 to 2011 to 2016 to 2017 (Pebody *et al*., 2018b). In the 65 to 74 year olds age group, this analysis showed significant effectiveness for all influenza, A(H1N1)pdm09, influenza B and some evidence of protection against A(H3N2). Above the age of 75 years old, however, pooled estimates were unable to demonstrate any significant effectiveness across all seasons and for all the influenza virus types.

In recognition of the low effectiveness of standard influenza vaccines against A(H3N2), especially in the elderly, several approaches are being used to try and mitigate the effects of immunosenescence and/or egg adaptation (where the vaccine viruses acquire mutations to enable them to grow well in eggs). In August 2017 an adjuvanted trivalent inactivated vaccine (aTIV) gained marketing authorisation in the UK for use in those aged 65 years and older. The aTIV has been licensed in some countries in Europe since 1997 and in the USA since 2015. A quadrivalent formulation of the adjuvanted vaccine (aQIV,) was granted licensure in May 2020 for use in those aged 65 years and older. There is evidence that the adjuvanted vaccine has higher immunogenicity and higher effectiveness than non-adjuvanted vaccines in the elderly (Van Buynder *et al*., 2013, Dominich *et al*., 2017). Since December 2018, a high dose TIV (TIV-HD), has also become licensed for this age group.

TIV-HD, which contains 4 times the antigen content of standard TIV, has been licensed in the USA since 2009. TIV-HD produces a stronger immune response and is more effective in preventing flu in adults 65 years of age and older compared with standard-dose vaccine (DiazGranados *et al*., 2014); another study found that TIV-HD vaccine was also associated with a lower risk of hospital admissions in this age group (Gravenstein *et al*., 2017).

In October 2017 and June 2018, JCVI reviewed the evidence on aTIV and TIV-HD vaccines respectively and saw mathematical modelling by PHE that suggested that, even under quite conservative estimates of improved effectiveness, both vaccines would be more cost-effective than unadjuvanted egg-based vaccine in those aged 65 years and over (JCVI., October 2017; JCVI., June 2018). Data from surveillance of the UK 2018 to 2019 season suggests aTIV in older adults offers protection against primary care attended infection and against hospitalisation (Pebody *et al*. 2020a; Pebody *et al*. 2020b).

Given the declining influenza vaccine effectiveness against A(H3N2) seen in all age groups in seasons approaching 2017 to 2018, culminating in non-significant effectiveness in all age groups during 2017 to 2018, in October 2018 the JCVI also reviewed information on the quadrivalent cell cultured inactivated vaccine (QIVc,). QIVc, which is licensed for use in adults and children from 2 years of age, is an inactivated vaccine made from influenza virus which is grown in mammalian cells and does not require isolation and manufacture using eggs. Cell cultured vaccines such as QIVc should overcome some of the issues associated with egg-adaptation seen in vaccines which use virus grown in eggs (QIVe and TIVe) and which alters the antigenic profile of the A(H3N2) egg propagated vaccine virus compared with the wild type reference strain. Data from the A(H3N2) dominated 2017 to 2018 USA flu season suggested a slight advantage in terms of effectiveness (Izurieta *et al*., 2019) for QIVc compared with QIVe in the elderly. However data from the USA 2018 to 2019 season (dominated by A(H1N1)pdm09 and A(H3N2)) (Izurieta *et al*., 2020a) and the USA 2019 to 2020 influenza B-Victoria and A(H1N1)pdm09-dominated season found no difference (Izurieta *et al*., 2020b).

Another vaccine which does not require eggs in its manufacture is the recombinant quadrivalent influenza vaccine (QIVr) which uses recombinant proteins of the haemagglutinin subunit expressed in insect cells. This vaccine has been used in the US since 2013. The potential use of QIVr, now licensed in the UK for use in those aged 18 years and above, was discussed by JCVI in June 2020. QIVr was shown to provide superior protection to egg-based vaccine in older adults in a US trial over the 2014 to 2015 season, though was not conclusive in those 65 years and older (Dunkle *et al*., 2017). QIVr was found moderately more effective in older adults than other vaccines in the US 2019 to 2020 season (Izurieta 2020b).

JCVI (September 2021) have advised that in those aged 65 years and over aQIV, QIVr and QIV-HD are the preferred vaccines and if these are not available then QIVc is considered an acceptable alternative.

JCVI have advised the use of QIVr and QIVc for vaccination of adults aged 18 to less than 65 years of age in an at-risk group. QIVe can also be considered for use in this age group if other options are not available. The JCVI have advised that for children aged 2 to less than 18 years of age in an at-risk group for whom LAIV is not suitable, QIVc is the preferred choice followed by QIVe (JCVI., October 2020).

For adults aged 50 to 64 years old not in a clinical risk group who are offered NHS influenza vaccination, JCVI has advised QIVe is suitable if this supports prioritising more vulnerable cohorts for vaccines considered most effective (JCVI December 2021). See section 'The Influenza immunisation programme during the COVID-19 pandemic' for further details.

International evidence continues to accumulate on the effectiveness of the newer vaccines (ECDC 2020). JCVI keeps its advice on seasonal influenza vaccines under regular review. The latest JCVI advice on seasonal influenza vaccines is available on the JCVI webpage at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#influenza-vaccines-jcvi-advice. Specific advice on those eligible for flu vaccination and which vaccines are suitable for use in eligible groups each season is published in the Annual influenza vaccination programme letters.

Storage (see Chapter 3)

Influenza vaccines should be stored in their original packaging at +2°C to +8°C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Efficacy, safety and quality may be adversely affected if vaccines are not stored in the temperatures specified in the license (see individual product's summary of product characteristics (SmPC)). Freezing may also cause increased reactogenicity and a loss of potency for some vaccines and can also cause hairline cracks in the container, leading to contamination of the contents.

LAIV may be left out of the refrigerator/removed from the cold chain for a maximum period of 12 hours at a temperature not above 25°C as indicated in the SmPC. If the vaccine has not been used after this 12-hour period, it should be disposed of.

Presentation

Inactivated influenza vaccines for intramuscular administration are supplied as suspensions in pre-filled syringes. They should be shaken well before they are administered.

LAIV is supplied as a nasal spray suspension in a special applicator.

Dosage and schedule

The dosages and schedules for the influenza vaccines should be given according to the recommendations for the use of the vaccine (see later).

Children aged 6 months to under 9 years who are in clinical risk groups and have not received influenza vaccine previously should be offered a second dose of vaccine. Children who have received 1or more doses of any influenza vaccine before (including pandemic monovalent influenza vaccine) should be considered as previously vaccinated (see later section on children).

JCVI has advised that children aged 2 years to under 9 years of age who are not in a clinical risk group, only require a single dose of LAIV irrespective of whether they have received influenza vaccine previously. This advice differs from that in the SmPC for LAIV. Healthy children under 9 years whose parents request they receive IIV instead of LAIV should be offered a single dose, even if they have not previously received influenza vaccine. The same applies to healthy children who cannot receive LAIV due to contraindications.

Administration

The inactivated influenza vaccines should normally be given into the deltoid muscle in the upper arm (or anterolateral thigh in infants) preferably by intramuscular injection.

There is a lack of evidence that the subcutaneous route of vaccination is any safer than the intramuscular route in people taking anticoagulants. The subcutaneous route can itself be associated with an increase in localised reactions.

Individuals on stable anticoagulation therapy, including individuals on warfarin who are up-to-date with their scheduled International Normalised Ratio (INR) testing and whose latest INR was below the upper threshold of their therapeutic range, can receive intramuscular vaccination. A fine needle (23 or 25 gauge) should be used for the vaccination, followed by firm pressure applied to the site (without rubbing) for at least 2 minutes. If in any doubt, consult with the clinician responsible for prescribing or monitoring the individual's anticoagulant therapy.

Individuals with bleeding disorders may be vaccinated intramuscularly if, in the opinion of a doctor familiar with the individual's bleeding risk, vaccines or similar small volume intramuscular injections can be administered with reasonable safety by this route. If the individual receives medication/treatment to reduce bleeding, for example treatment for haemophilia, intramuscular vaccination can be scheduled shortly after such medication/ treatment is administered. A fine needle (23 or 25 gauge) should be used for the vaccination, followed by firm pressure applied to the site (without rubbing) for at least 2 minutes (ACIP 2022). The individual/parent/carer should be informed about the risk of haematoma from the injection.

The live attenuated influenza vaccine (LAIV) is administered by the intranasal route and is supplied in an applicator that allows a divided dose to be administered in each nostril (total dose of 0.2ml, 0.1ml in each nostril). The device allows intranasal administration to be performed without the need for additional specialist training. Administration does not need to be repeated if the patient sneezes or blows their nose following administration. For advice on administering LAIV to those with heavy nasal congestion see the precautions section of this chapter.

As a wide variety of influenza vaccines are on the UK market each year, it is especially important that the exact brand of vaccine, batch number and site at which each vaccine is given is accurately recorded in the patient records. Where the vaccine is given for occupational reasons, it is recommended that the employer keep a vaccination record. It is important that vaccinations given either at a general practice or elsewhere (for example, at community pharmacies, or antenatal clinics) are recorded on appropriate health records for the individual (using the appropriate clinical code) in a timely manner. If given outside of general practice, a record of vaccination should be returned to the patient's general practice to allow clinical follow up if needed and to avoid duplicate vaccination. Electronic point of care data capture systems may support this.

Recommendations for the use of the vaccines

The objectives of the influenza immunisation programme are to protect those who are most at risk of serious illness or death should they develop influenza and to reduce transmission of the infection, thereby contributing to the protection of vulnerable patients who may have a suboptimal response to their own immunisations.

To facilitate this, general practitioners are required to proactively identify all those for whom influenza immunisations are indicated and to compile a register of those patients for whom influenza immunisation is recommended. Sufficient vaccine can then be ordered in advance and patients can be invited to planned immunisation sessions or appointments. Given that some influenza vaccines are restricted for use in particular age groups, the SmPCs for individual products should always be referred to when ordering vaccines to ensure that they can be given appropriately to particular patient age groups.

Research has identified processes at GP surgeries that are associated with higher uptake of influenza vaccine (Dexter *et al*., 2012). This included, having a named individual at the surgery responsible for the influenza immunisation programme; update and maintenance of an accurate register of patients eligible for influenza immunisation and direct contact with eligible patients inviting them for immunisation. See also NICE guideline (2018) NG103.

Patients should be advised that many other organisms cause respiratory infections similar to influenza during the influenza season, for example COVID-19 (SARS-CoV-2), common cold viruses and respiratory syncytial virus. Influenza vaccine will not protect against these diseases.

Influenza vaccine should be offered, ideally before influenza viruses start to circulate, to:

- all those aged 65 years or older (for definition please see the annual flu letter for the coming/current season)
- all those aged 6 months or older in the clinical risk groups shown in Table 19.4
- other children in cohorts eligible for vaccination as part of the children's flu programme. (see below)

During the COVID-19 epidemic, additional groups have been eligible for influenza vaccination. See the section above on influenza vaccination during the COVID-19 pandemic.

Table 19.4 Clinical risk groups who should receive the influenza immunisation. Influenza vaccine should be offered to people in the clinical risk categories set out below.

Clinical risk category	Examples (this list is not exhaustive and decisions should be based on clinical judgement)
Chronic respiratory disease	Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children who have previously been admitted to hospital for lower respiratory tract disease. See precautions section on LAIV.
Chronic heart disease and vascular disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease. This includes individuals with atrial fibrillation, peripheral vascular disease or a history of venous thromboembolism.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis.
Chronic neurological disease (included in the DES directions for Wales)	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological or neuromuscular disease (for example polio syndrome sufferers). Clinicians should offer immunisation, based on individual assessment, to clinically vulnerable individuals including those with cerebral palsy, severe or profound and multiple learning disabilities (PMLD), Down's syndrome, multiple sclerosis, dementia, Parkinson's disease, motor neurone disease and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.
Diabetes and adrenal insufficiency	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet-controlled diabetes. Addison's disease, secondary or tertiary adrenal insufficiency requiring steroid replacement.
Immunosuppression (see contraindications and precautions section on live attenuated influenza vaccine)	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, people living with HIV (at all stages), multiple myeloma or genetic disorders affecting the immune system (for example IRAK-4, NEMO, complement disorder, SCID). Individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-TNF- alemtuzumab, ofatumumab, rituximab, patients receiving protein kinase inhibitors or PARP inhibitors, and individuals treated with steroid sparing agents such as cyclophosphamide and mycophenolate mofetil. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age), or for children under 20kg, a dose of 1mg or more per kg per day. Anyone with a history of haematological malignancy, including leukaemia, lymphoma, and myeloma and those with systemic lupus erythematosus and rheumatoid arthritis, and psoriasis who may require long term immunosuppressive treatments. Some immunocompromised patients may have a suboptimal immunological response to the vaccine.

Clinical risk category	Examples (this list is not exhaustive and decisions should be based on clinical judgement)
Asplenia or dysfunction of the spleen	This also includes conditions such as homozygous sickle cell disease, hereditary spherocytosis, thalassemia major and coeliac syndrome that may lead to splenic dysfunction.
Pregnant women	Pregnant women at any stage of pregnancy (first, second or third trimesters). See precautions section on live attenuated influenza vaccine.
Morbid obesity (class III obesity)*	Adults with a Body Mass Index ≥40 kg/m².

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

The list above is not exhaustive, and the medical practitioner should apply clinical judgment to take into account the risk of influenza exacerbating any underlying disease that a patient may have, as well as the risk of serious illness from influenza itself. Influenza vaccine should be offered in such cases even if the individual is not in the clinical risk groups specified above.

Other risk groups

Vaccination should also be offered to household contacts of immunocompromised individuals, therefore individuals who expect to share living accommodation on most days over the winter and therefore for whom continuing close contact is unavoidable. This may include carers (see below).

In addition to the above, immunisation should be provided to healthcare and social care workers in direct contact with patients/clients to protect them and to reduce the transmission of influenza within health and social care premises, to contribute to the protection of individuals who may have a suboptimal response to their own immunisations, and to avoid disruption to services that provide their care. This would include:

- health and social care staff directly involved in the care of their patients or clients
- those living in long-stay residential care homes or other long-stay care facilities where rapid spread is likely to follow introduction of infection and cause high morbidity and mortality (this does not include prisons, young offender institutions, university halls of residence etc.)
- those who are in receipt of a carer's allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill. Vaccination should be given on an individual basis at the GP's discretion in the context of other clinical risk groups in their practice
- others involved directly in delivering health and social care such that they and vulnerable patients/clients are at increased risk of exposure to influenza (further information is provided in guidance from UK health departments)

Children

Studies suggest that 2 doses of inactivated influenza vaccine may be required to achieve adequate antibody levels in younger children who have not received influenza vaccine before (Allison *et al.*, 2006; Neuzil *et al.*, 2006; Ritzwoller *et al.*, 2005; Shuler *et al.*, 2007;

Wright *et al*., 1977). LAIV has been shown to provide greater protection for children than inactivated influenza vaccine (Belshe *et al*., 2007; Ashkenazi *et al*., 2006; Fleming *et al*., 2006) and studies have also shown meaningful efficacy after a single dose of LAIV in previously unvaccinated children (Bracco Neto *et al*., 2009; Block *et al*., 2009). Given this, JCVI has advised, as set out below, the use of different schedules of influenza vaccine for children depending on their age, the clinical indications, the type of vaccine offered and whether they have received influenza vaccine previously. This advice differs from some of the SmPCs. LAIV and the inactivated influenza vaccines are interchangeable; a second dose, if required, should be given at least 4 weeks after the first dose in accordance with the manufacturer's SmPC for that vaccine.

Children aged 2 to less than 17 years old NOT IN clinical risk groups

Eligibility for vaccination may differ across the UK countries. Please see the respective annual flu letters for England and the Devolved Administrations for the cohorts of children that are eligible for influenza vaccination for the coming/current season.

A single dose of LAIV should be offered per season, unless contraindicated, irrespective of whether influenza vaccine has been received previously.

Children aged 6 months to less than 18 years of age who are household contacts of immunocompromised individuals.

Children who are household contacts of immunocompromised individuals should be vaccinated in accordance with the advice on children in clinical risk groups. Inactivated vaccine may need to be given instead of LAIV. See the section on immunosuppression and people living with HIV.

Children aged 6 months to less than 2 years of age IN clinical risk groups

These children should be offered the recommended inactivated quadrivalent influenza vaccine. Those who have not received influenza vaccine previously should be offered a second dose of vaccine, at least 4 weeks later. The inactivated influenza vaccines are interchangeable; the second dose, if required, should be given at least 4 weeks after the first dose in accordance with the manufacturer's SmPC for that vaccine. LAIV is not licensed or recommended for children under 2 years of age. QIVc is not licensed for use under 2 years of age. For egg-allergic children under 2 years it is advised that QIVc is offered off-label.

It is important that preterm infants who have risk factors have their immunisations at the appropriate chronological age. Influenza immunisation should be considered after the child has reached 6 months of age.

Children aged 2 to less than 18 years of age IN clinical risk groups

Children aged 2years to less than 18 years in clinical risk groups should be offered LAIV unless it is medically contraindicated or otherwise unsuitable (see contraindications and precautions sections). Those children who have never received influenza vaccine before and are aged between 2 and less than 9 years should be offered a second dose of LAIV at least 4 weeks later. If LAIV is unavailable for this second dose (due to batch expiry) an inactivated influenza vaccine can be given.

For those children in clinical risk groups for whom LAIV is medically contraindicated, a suitable quadrivalent inactivated influenza vaccine should be offered. Children aged 2 to less than 9 years old who have not received influenza vaccine previously should be offered a second dose of the vaccine at least 4 weeks later.

Table 19.5 summarises the advice on influenza vaccination for children.

Table 19.5 Influenza vaccination for children under 18 years old

Eligible cohort	Children in clinical risk groups and children who are household contacts of immunocompromised individuals	Children not in clinical risk groups[1]
6 months to less than 2 years old	Offer suitable quadrivalent inactivated flu vaccine. Those who have not received flu vaccine before should be offered 2 doses (given at least 4 weeks apart).	Not applicable.
2 years to less than 9 years old	Offer LAIV (unless medically contraindicated[2]) Those who have not received flu vaccine before should be offered 2 doses (given at least 4 weeks apart).	Offer LAIV[1]
Children aged 9 years to less than 18 years old	Offer LAIV (unless medically contraindicated[2]).	Offer LAIV[1]

1 Please see the respective annual flu letters for England and the Devolved Administrations for the cohorts of children not in clinical risk groups that are eligible for influenza vaccination for the coming/current season.

2 If LAIV is medically contraindicated or otherwise unsuitable, then offer quadrivalent inactivated flu vaccine.

Additional groups eligible for influenza immunisation during the COVID-19 pandemic

In July 2020, JCVI advised on additional influenza vaccine and extensions for the influenza programme as temporary measures for the 2020 to 2021 influenza season. The aim of the proposed measures outlined below was to protect the most vulnerable and alleviate potential pressure on the NHS during the influenza season when influenza, SARS-CoV-2 and other respiratory pathogens might be expected to be co-circulating.

The Committee emphasised the importance of increasing vaccine uptake as much as possible in the most vulnerable groups and for health and social care workers. The Committee also supported extending vaccination in the childhood programme into secondary school age and to all adults aged between 50 and 64 years of age, as temporary measures for the 2020 to 2021 influenza season. In addition, eligibility was extended to household contacts of the shielded population defined on medical grounds as extremely vulnerable for COVID-19. In August 2020, JCVI agreed that it would be reasonable to continue with this enhanced programme during the following winter (2021 to 2022).

As a result, the influenza programme for 2021 to 2022 included the offer of vaccination to 50 to 64 year olds, expansion of the childhood programme further into secondary schools (Years 7 to 11) and increasing uptake as much as possible for those groups routinely offered vaccination including health and social care workers.

In December 2021, JCVI advised that there remained uncertainty around 2022 to 2023 influenza activity and endorsed the previous JCVI recommendation of prioritising secondary school expansion and its pandemic-time advice that vaccination of all 50 to 64 year olds would be acceptable if funding was available.

For more information see: www.gov.uk/government/publications/national-flu-immunisation-programme-plan. Please see the respective Chief Medical Officer letters for the Devolved Administrations (see links on page 8).

Co-administration of influenza and other vaccines

Inactivated influenza vaccines can be given at the same time as other vaccines. Intramuscular vaccines should be given at separate sites, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003).

LAIV can also be given at the same time as other live or inactivated vaccines. Although it was previously recommended that, where vaccines cannot be administered simultaneously; a 4-week interval should be observed between live viral vaccines, JCVI have advised that no specific intervals need to be observed between LAIV and other live vaccines (see Chapter 6).

COVID-19 and Influenza vaccines

A UK study of co-administration of AstraZeneca and Pfizer BioNTech COVID-19 vaccines with inactivated influenza vaccines confirmed acceptable immunogenicity and reactogenicity (Lazarus *et al*, 2021). In contrast, a study of co-administration of Novavax COVID-19 vaccine with inactivated influenza, did show some attenuation of the antibody response to COVID-19 (Toback et al, 2022). Although the clinical significance of this is unclear, administration of Novavax COVID-19 vaccine should be separated from administration of influenza vaccine by at least 7 days. For other COVID-19 vaccines, where co-administration does occur, patients should be informed about the likely timing of potential adverse events relating to each vaccine. If the vaccines are not given together, they can be administered at any interval, although separating the vaccines by a day or 2 will avoid confusion over systemic side effects.

LAIV nasal spray vaccine can be given at the same time as COVID-19 vaccines. LAIV triggers an immune response in the nasal mucosa. This is unlikely to interfere with the body's response to COVID-19 vaccines. Similarly, it's unlikely that the response to LAIV will be affected by the immune response to COVID-19 vaccine. Side effects of the nasal flu spray are very mild and short-lived and are unlikely to be in any way affected by the COVID-19 vaccine.

Shingles and influenza vaccine

Zostavax® can be given at the same time as inactivated influenza vaccination. Shingrix® can be given concomitantly with inactivated influenza vaccine. Because of the absence of data on co-administration of Shingrix® vaccine with adjuvanted influenza vaccine (aQIV), it should not be routine to offer appointments to give this vaccine at the same time as the adjuvanted influenza vaccine. Based on current information, scheduling should ideally be separated by an interval of at least 7 days to avoid incorrect attribution of potential adverse events. Where individuals attend requiring both vaccines, however, and require rapid protection or are considered likely to be lost to follow up, co-administration may still be considered.

Contraindications

The SmPCs for individual products should always be referred to when deciding which vaccine to give. There are very few individuals who cannot receive any influenza vaccine. When there is doubt, appropriate advice should be sought promptly from the local NHS England screening and immunisation team, a consultant in communicable disease control/ health protection or a specialist consultant, so that the period the individual is left unvaccinated is minimised.

None of the influenza vaccines should be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of the vaccine, or
- a confirmed anaphylactic reaction to any component of the vaccine (other than ovalbumin – see precautions)

Confirmed anaphylaxis is rare (see Chapter 8 for further information). Other allergic conditions such as rashes may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between true anaphylaxis and other events that are either not due to the vaccine or are not life threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and the circumstances in which they could be given (see Chapter 6 for further information). The risk to the individual of not being immunised must be taken into account.

LAIV should not be given to children or adolescents who are clinically severely immunocompromised due to conditions or immunosuppressive therapy such as: acute and chronic leukaemias; lymphoma; cellular immune deficiencies; and HIV infection not suppressed by antiretroviral therapy; and high dose corticosteroids. It is not contraindicated for use in children or adolescents living with HIV who are receiving antiretroviral therapy and attaining viral suppression; or those who are receiving topical corticosteroids, inhaled corticosteroids or low-dose systemic corticosteroids, or those receiving corticosteroids as replacement therapy, for example for adrenal insufficiency. It is contraindicated in children and adolescents receiving salicylate therapy (other than for topical treatment of localised conditions) because of the association of Reye's syndrome with salicylates and wild-type influenza infection as described in the SmPC for LAIV.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

There are no data on the effectiveness of LAIV (when given to children with a heavily blocked or runny nose (rhinitis) attributable to infection or allergy. As heavy nasal congestion might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration until resolution of the nasal congestion should be considered, or if appropriate, an intramuscularly administered influenza vaccine could be given instead.

Children with cochlear implants can be given LAIV safely although ideally not in the week prior to implant surgery or for 2 weeks afterwards, or if there is evidence of on-going cerebrospinal fluid leak.

Pregnancy

Pregnant women should be offered inactivated influenza vaccine as the risk of serious illness from influenza is higher in pregnant women (Pebody *et al*., 2010). In addition, a number of studies show that influenza vaccination during pregnancy provides passive immunity against influenza to infants in the first few months of life following birth (Benowitz *et al*., 2010; Eick *et al*., 2010; Zaman *et al*., 2008; Poehling *et al*., 2011). A study showed that influenza vaccination reduced the likelihood of prematurity and smaller infant size at birth associated with influenza infection (Omer *et al*., 2011).

A review of studies on the safety of influenza vaccine in pregnancy concluded that inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy (Tamma *et al*., 2009). Data are more limited for LAIV. There is no evidence of risk with LAIV (Toback *et al*., 2012). The live viruses in LAIV have been attenuated (weakened) and adapted to cold so that they can only replicate at the lower temperatures found in the nasal passage. These live viruses cannot replicate efficiently elsewhere in the body and therefore there is no theoretical basis for concern about infection of the unborn foetus or the mother's lungs. Inactivated influenza vaccines are, however, preferred for those who are pregnant. There is no need to specifically ask about or test for pregnancy when offering LAIV to eligible girls or to advise avoidance of pregnancy in those who have been recently vaccinated.

Immunosuppression and people living with HIV

Individuals who have immunosuppression or are living with HIV (regardless of CD4 count) should be given influenza vaccine in accordance with the recommendations and contraindications above. These individuals may not make a full antibody response.

Consideration should also be given to the influenza vaccination of household contacts of immunocompromised individuals, this means individuals who expect to share living accommodation on most days over the winter and therefore for whom continuing close contact is unavoidable.

There is a theoretical potential for transmission of live attenuated influenza virus in LAIV to immunocompromised contacts for 1 to 2 weeks following vaccination. In extensive use of the LAIV in the UK (over 10 million doses), there have been no reported instances of illness or infections from the vaccine virus among immunocompromised patients inadvertently exposed. However where close contact with very severely immunocompromised patients (for example bone marrow transplant patients requiring isolation) is likely or unavoidable (for example, household members), appropriate alternative inactivated influenza vaccines should be considered.

Further guidance is provided by the Royal College of Paediatrics and Child Health (https://www.rcpch.ac.uk/), the British HIV Association (BHIVA) guidelines on the use of vaccines in HIV-positive adults (BHIVA, 2015) and the Children's HIV Association (CHIVA) immunisation guidelines http://www.chiva.org.uk/guidelines/immunisation/

Severe asthma or active wheezing

JCVI have advised (2019) that, on the basis of recent data, children with asthma on inhaled corticosteroids may safely be given LAIV, irrespective of the dose prescribed.

LAIV is not recommended for children and adolescents currently experiencing an acute exacerbation of symptoms including those who have had increased wheezing and/or needed additional bronchodilator treatment in the previous 72 hours. Such children should be offered a suitable inactivated influenza vaccine to avoid a delay in protection.

There are limited safety data in children who require regular oral steroids for maintenance of asthma control, or have previously required intensive care for asthma exacerbation – such children should only be given LAIV on the advice of their specialist. As these children may be at higher risk from influenza infection, those who cannot receive LAIV should receive a suitable inactivated influenza vaccine.

Children with significant asthma and aged under 9 years who have not been previously vaccinated against influenza will require a second dose (of either LAIV or inactivated vaccine as appropriate).

Egg allergy

In all settings providing vaccination, facilities should be available and staff trained to recognise and treat anaphylaxis (see Chapter 8). Inactivated influenza vaccines that are egg-free or have a very low ovalbumin content (<0.12 micrograms/ml - equivalent to <0.06 micrograms for a 0.5 ml dose) are available and studies show they may be used safely in individuals with egg allergy (des Roches *et al*., 2012). LAIV which previously had an upper ovalbumin limit of 1.2 micrograms/ml, has also been shown (JCVI, 2015) to be safe for use in egg-allergic children. The ovalbumin content of LAIV has been further reduced since 2016 (≤0.024 micrograms per 0.2ml dose). The ovalbumin content of influenza vaccines is published prior to the influenza season. www.gov.uk/government/publications/influenza-vaccines-marketed-in-the-uk

JCVI has advised (JCVI, 2015) that children with an egg allergy – including those with previous anaphylaxis to egg – can be safely vaccinated with LAIV in any setting (including primary care and schools). The only exception is for children who have required admission to intensive care for a previous severe anaphylaxis to egg, for whom no data are available; such children are best given a vaccine in the hospital setting. In children in this group aged 2 years and over, LAIV remains the preferred vaccine as the intranasal route is less likely to cause systemic reactions. For those six months to 2 years, an inactivated influenza vaccine with a very low ovalbumin content (less than 0.12 micrograms/ml) is suitable. JCVI has advised that egg-allergic children aged less than 2 years can be offered the quadrivalent inactivated egg-free vaccine, QIVc. This is an off-label recommendation which is supported by unpublished data which shows non inferiority of immunogenicity and a very similar safety profile for QIVc compared with QIVe in children less than 2 years old.

Children with egg allergy (less severe than anaphylaxis requiring intensive care) but who also have another condition which contraindicates LAIV can be offered in any setting an inactivated influenza vaccine with a very low ovalbumin content (less than 0.12 micrograms/ml). Children in a clinical risk group and aged under 9 years who have not been previously vaccinated against influenza will require a second dose (of either LAIV or inactivated vaccine as appropriate). Children over the age of 2 years with egg allergy can also be given the cell-grown quadrivalent inactivated egg-free vaccine (QIVc), which is licensed for use in this age group.

Adult patients with egg allergy can be immunised in any setting using an inactivated influenza vaccine with an ovalbumin content less than 0.12 micrograms/ml (equivalent to 0.06 micrograms per 0.5 ml dose), excepting those with severe anaphylaxis to egg which has previously required intensive care. These adults should be offered an egg-free vaccine. If this is not possible, they should be referred to a specialist for assessment with regard to receiving immunisation in hospital. Egg-free vaccines licensed in adults are the cell-grown quadrivalent inactivated vaccine (QIVc), and the recombinant quadrivalent egg-free vaccine (QIVr).

Use with antiviral agents against influenza

There is a potential for influenza antiviral agents to lower the effectiveness of LAIV. Therefore, influenza antiviral agents and LAIV should not be administered concomitantly. LAIV should be delayed until 48 hours following the cessation of treatment with influenza antiviral agents.

Administration of influenza antiviral agents within 2 weeks of administration of LAIV may adversely affect the effectiveness of the vaccine.

Exposure of healthcare professionals to LAIV viruses

In theory, healthcare workers may have low level exposure to LAIV viruses during administration of the vaccine and/or from recently vaccinated patients. The vaccine viruses are cold-adapted and attenuated and are unlikely to cause symptomatic influenza. In the US, where there has been extensive use of LAIV, no transmission of vaccine virus in healthcare settings has ever been reported and there have been no reported instances of illness or infections from the vaccine virus among healthcare professionals inadvertently exposed. Thus, the CDC has considered that the risk of acquiring vaccine viruses from the environment is unknown but is probably low (CDC, 2013). As a precaution, however, very severely immunosuppressed individuals should not administer LAIV. Other healthcare workers who have less severe immunosuppression or are pregnant, should follow normal clinical practice to avoid inhaling the vaccine and ensure that they themselves are appropriately vaccinated.

Inadvertent administration of LAIV

If an immunocompromised individual receives LAIV then the degree of immunosuppression should be assessed. If the patient is severely immunocompromised, antiviral prophylaxis should be considered, otherwise they should be advised to seek medical advice if they develop flu-like symptoms in the 4 days (the usual incubation period) following administration of the vaccine. If antivirals are used for prophylaxis or treatment, then in order to maximise their protection in the forthcoming flu season, the patient should also be offered inactivated influenza vaccine. This can be given straight away.

Adverse reactions

Pain, swelling or redness at the injection site, low grade fever, malaise, shivering, fatigue, headache, myalgia and arthralgia are among the commonly reported symptoms after intramuscular or intradermal vaccination. A small painless nodule (induration) may also form at the injection site. These symptoms usually disappear within 1 to 2 days without treatment. Nasal congestion/rhinorrhoea, reduced appetite, weakness and headache are common adverse reactions following administration of LAIV.

Immediate reactions such as urticaria, angio-oedema, bronchospasm and anaphylaxis can occur.

The following adverse events have been reported very rarely after influenza vaccination over the past 30 years but no causal association has been established: neuralgia, paraesthesia, convulsions (see note below) and transient thrombocytopenia, vasculitis with transient renal involvement and neurological disorders such as encephalomyelitis.

Guillain- Barré syndrome (GBS) has been reported very rarely after immunisation with influenza vaccine, one case per million people vaccination in one US study (Laskey *et al*., 1998). This association was not found in other studies (Hurwitz *et al*., 1981; Kaplam *et al*., 1982; Roscelli *et al*., 1991) including a large study in the UK (Stowe *et al*., 2009). The latter study found a strong association between GBS and influenza-like illness. This increased risk of GBS after influenza-like illness, if specific to infection with influenza virus, together with the absence of a casual association with influenza vaccine suggests that influenza vaccine should protect against GBS (Stowe *et al*.,2009).

Side effects and adverse reactions associated with the influenza vaccines Viroflu® and Pandemrix® have been previously documented. Viroflu® (Janssen- Cilag Ltd, formerly Crucell) may be associated with a higher than expected rate of fever in children aged under 5 years. An increased risk of narcolepsy after vaccination with the ASO3 adjuvanted pandemic A/H1N1 2009 vaccine Pandemrix® was identified in England (Miller *et al*., 2013) consistent with findings first identified in Finland and Sweden (Nohynek *et al*., 2010; Partinen *et al*., 2010). Viroflu® and Pandemrix® are no longer used in the UK influenza immunisation programme.

All serious suspected reactions in adults and all suspected reactions in children following influenza vaccines should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card scheme at https://www.mhra.gov.uk/yellowcard.

Regardless of age, all suspected reactions should also be reported for black triangle products. The black triangle is a standard symbol added to the product information of a vaccine during the earlier stages of its introduction, to encourage reporting of all suspected adverse reactions.

The following vaccines carry a black triangle symbol (▲):

- adjuvanted quadrivalent inactivated influenza vaccine (aQIV, made by Seqirus)
- quadrivalent cell cultured inactivated influenza vaccine (QIVc made by Seqirus),
- recombinant quadrivalent inactivated influenza vaccine (QIVr, Supemtek, made by Sanofi Pasteur) and Quadrivalent Influvac® sub-unit Tetra, an inactivated egg-based influenza vaccine (a QIVe made by Viatris, formerly Mylan)
- high-dose quadrivalent inactivated influenza vaccine (QIV-HD)

Febrile convulsions and fever

One inactivated influenza vaccine (Fluvax by bioCSL marketed in the UK by Pfizer as Enzira® or influenza vaccine (split virion, inactivated) has been associated with a high rate of febrile convulsions in children under 5 years of age in other countries. The SmPC for Enzira® also indicates that a high rate of fever was reported in the age group aged 5 to under 9 years. Due to the risk of febrile convulsions, the indication for Enzira® is restricted to use in adults and children aged 5 years and older. This vaccine will not be part of the central supply for use in children and is no longer available for purchase.

There remains no evidence that other influenza vaccines used in the UK are associated with a similar risk of febrile convulsions in children (Stowe *et al*., 2011; Bryan and Seabroke, 2011).

Management of suspected cases, contacts and outbreaks

There are antiviral drugs available that can be used under certain circumstances to either prevent or treat influenza. NICE has issued guidance on the use of antiviral drugs for the prevention and treatment of influenza:

Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza

https://www.nice.org.uk/guidance/ta158

Amantadine, oseltamivir and zanamivir for the treatment of influenza:

http://guidance.nice.org.uk/TA168

It is always important to encourage and maintain good hand and respiratory hygiene which can help to reduce the spread of influenza.

Supplies

Demand for influenza vaccine sometimes increases unpredictably in response to speculation about influenza illness in the community. Therefore, it is recommended that practices order sufficient vaccine for their needs, based on their 'at risk' registers, well in advance of the immunisation season.

Information on supplies and how to order vaccines will be given in guidance provided separately by each of the 4 UK countries – see respective websites for details. LAIV and quadrivalent inactivated vaccines are purchased centrally for eligible children aged 6 months to less than 18 years. These vaccines should be ordered as per the usual mechanisms for the routine childhood immunisation programme (also see Chapter 3).

Arrangements for supply may differ between England and the Devolved Administrations.

Suppliers of influenza vaccines

AstraZeneca UK Ltd 0845 139 0000

GlaxoSmithKline 0800 221 441

MASTA 0113 238 7552

Sanofi Pasteur 0845 023 0440

Seqirus UK Ltd 08457 451500

Viatris (formerly Mylan) 0800 358 7468

A list of the influenza vaccines available in the UK is published ahead of the influenza season in the national flu immunisation programme plan for England (available at: https://www.gov.uk/government/collections/annual-flu-programme).

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