19

Influenza

The disease

Influenza is an acute viral infection of the respiratory tract. There are three 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 one to three 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 two to seven 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 six 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) and those with underlying health conditions such as respiratory or cardiac disease, chronic neurological conditions, or immunosuppression and 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). 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 (Lau *et al*., 2010). Influenza spreads rapidly, especially in closed communities. Most cases in the UK tend to occur during an eight- to ten-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.

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 1000 clinical cases (95% confidence limits 0.13 to 0.4 per 1000 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).

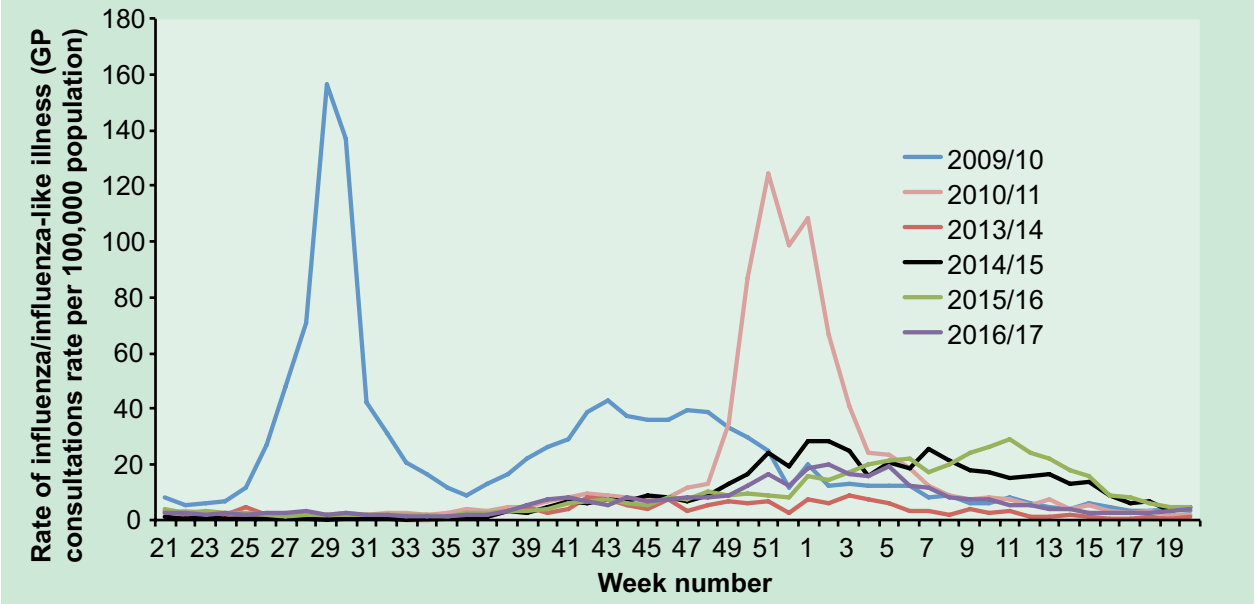

Figure 19.1 Rate of influenza/influenza-like illness episodes in England (weekly returns to Royal College of General Practitioners), 2009–11 to 2013–17 showing the variation in the timing and shape of influenza activity usually between weeks 37 and 15. However, much of the influenza A(H1N1) v pandemic 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. There may be differences in the epidemiology of influenza between the different countries in the UK. Data provided by PHE (formerly HPA) and RCGP.

The influenza A(H1N1)v strain continued to cause widespread illness during the 2010/11 influenza season. Despite the recent emergence of the influenza A(H1N1)v strain, conditions still exist for the emergence of future influenza strains with potential to lead to another pandemic (for example, from influenza A H5N1 or H7N9 strains).

Influenza B viruses are also subject to antigenic drift but with less frequent changes.

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 Public Health England (PHE, formerly Health Protection Agency (HPA)). Additional information for England is provided by the Royal College of General Practitioners (RCGP), for Scotland by 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 PHE. 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 and Wales range from not determined (in 2005-6 and 2006-7) to 10,351 (in 2008-9). The highest estimate in the past two decades was 24,797 for the 1999-2000 influenza season (Hardelid *et al*, 2013).

PHE 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 of data from fatal cases collected in England during the 2010/11 influenza season, when influenza A(H1N1)v 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 six months to under 65 years by clinical risk group in England, September 2010 – 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
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 two available age groups (from six months up to 15 years and from 16 to 64 years).

Table reproduced from *Surveillance of influenza and other respiratory viruses in the UK 2010-2011 report* by kind permission of PHE.

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)

* 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

*Denominator incomplete

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 (Fluenz® Tetra) 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.

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

Northern Ireland:
http://www.dhsspsni.gov.uk/index/phealth/professional/cmo_communications.htm

Scotland:
http://www.sehd.scot.nhs.uk/index.asp?name=&org=%25&keyword=&category=9&number=10&sort=tDate&order=DESC&Submit=Go

Wales:
http://gov.wales/topics/health/professionals/cmo/updates/?lang=en

The influenza vaccination

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) Fluenz® Tetra 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.

Most of the vaccines are prepared from viruses grown in embryonated hens' eggs, although cell based production is likely to become more important in future years.

Because of the changing nature of influenza viruses, 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 (http://www.who.int/influenza/en/).

Influenza vaccines are prepared using virus strains in line with the WHO recommendations. Some inactivated influenza vaccines are trivalent, containing two subtypes of influenza A and one B virus; however, quadrivalent vaccines that contain an additional B virus have now become routinely available.

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.

For children, LAIV and quadrivalent inactivated vaccines are centrally procured and supplied. For adults, a range of inactivated vaccines are available from suppliers for GPs to purchase, according to annual recommendations. All authorised influenza vaccines need to meet immunogenicity, safety and quality criteria set by the European Committee for Medicinal Products for Human Use (CHMP), with the assessment of expected efficacy based on meeting or exceeding indicated requirements of immunogenicity and/or efficacy dependent on the type of vaccine being assessed (EMA, 2016). A list of the influenza vaccines available in the UK is published ahead of the influenza season in the National immunisation programme plan (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.

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 2003-2004), 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 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.

With the exception of 2014/15, in most recent years, the vaccines have closely matched the influenza A viruses circulating during the influenza season. A recent meta-analysis, which included studies when the influenza virus strains in the trivalent 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). Since 2016/17 lower effectiveness against A(H3N2) has been attributed to the vaccines strains acquiring egg adaptive changes (Pebody *et al*., 2018).

The live attenuated influenza vaccine (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 recent 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 2015/16 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 2015/16 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*., 2017; Pebody *et al*., 2016). 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)

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 has been 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.

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 2016/17 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 have recently conducted an age stratified analysis of pooled primary care data since 2010/11 (in press). In the 65-74 year 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 (see below). In August 2017 an adjuvanted trivalent inactivated vaccine (ATIV) which at that time was known as Fluad® gained marketing authorisation in the UK for use in those aged 65 years and older. Since December 2018, and since December 2018, a high dose TIV (TIV-HD), Fluzone®, has also become licensed for this age group. The aTIV has been licensed in some countries in Europe since 1997 and in the USA since 2015. TIV-HD, which contains four times the antigen content of standard TIV, has been licensed in the USA since 2009. 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). 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 standard vaccine in those aged 65 years and over (JCVI., October 2017; JCVI., June 2018)

Given the declining influenza vaccine effectiveness against A(H3N2) seen in all age groups in recent seasons, culminating in non-significant effectiveness in all age groups during 2017/18, in October 2018 the JCVI also reviewed information on the quadrivalent cell cultured inactivated vaccine (QIVc), Flucelvax® Tetra. QIVc, which has been licensed for use in those aged nine years and over since December 2018, 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. Preliminary data from the 2018-19 USA flu season suggested a slight advantage in terms of effectiveness (Izurieta *et al*., 2018) for QIVc compared with QIVe in the elderly.

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 (Flublok®) has been used in the US since 2013 and is licensed in the US for use in those aged 18 years and above. The potential use of QIVr in the UK 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 2014-15 season (Dunkle *et al* 2017). JCVI have therefore advised that QIVr, QIVc, aTIV and HD TIV are suitable for use in those aged 65 years and over and are preferable to standard egg based inactivated trivalent and quadrivalent vaccines (TIVe and QIVe). JCVI have also advised that QIVr, QIVc and QIVe are suitable vaccines for use in those less than 65 years of age and in an at-risk group (JCVI., October 2018).

JCVI keeps under regular review its advice on seasonal influenza vaccines. 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 and can be accessed here. 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 letter (see page 6 on annual flu communications).

Storage (also refer to Chapter 3)

Vaccines should be stored in the 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. 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.

Fluenz® Tetra 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 SPC. 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.

Fluenz® Tetra 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).

Some of the product characteristics (SPCs) for intramuscular inactivated influenza vaccines indicate that young children can be given a 0.25ml or 0.5ml dose. JCVI has advised where these alternative doses are indicated in the SPC, the 0.5ml dose of intramuscular inactivated influenza vaccines should be given to infants aged six months or older and young children because there is evidence that this dose is effective in young children (Heinonen *et al.*,2011).

Children aged six months to under nine years who are in clinical risk groups and have not received influenza vaccine previously should be offered a second dose of vaccine. JCVI has advised that children aged two years to under nine 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 SPC for Fluenz® Tetra. Children who have received one or more doses of any influenza vaccine before (including pandemic monovalent influenza A(H1N1)v vaccine) should be considered as previously vaccinated (see later section on children).

Administration

The inactivated influenza vaccines should normally be given into the upper arm (or anterolateral thigh in infants) preferably by intramuscular injection. Influenza vaccines licensed for intramuscular or subcutaneous administration may alternatively be administered by the subcutaneous route.

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 2018). 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 (Fluenz® Tetra) 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 training. Administration of either dose does not need to be repeated if the patient sneezes or blows their nose following administration. There are no data on the effectiveness of Fluenz® Tetra 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 alternative intramuscularly administered influenza vaccine.

Inactivated influenza vaccines can be given at the same time as other vaccines. 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 four-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). 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).

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 and to avoid duplicate vaccination.

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 SPCs 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.

Patients should be advised that many other organisms cause respiratory infections similar to influenza during the influenza season, e.g. the common cold 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 six months or older in the clinical risk groups shown in Table 19.4
- children not in clinical risk groups that are eligible for vaccination as part of the ongoing phased roll out of the extension of the programme to all children aged two to less than seventeen years old*

* Note: please see the respective annual flu letters for England and the Devolved Administrations for specific details on the cohorts of children that are eligible for influenza vaccination.

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 live attenuated influenza vaccine
Chronic heart disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease.
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 disease (e.g. polio syndrome sufferers). Clinicians should offer immunisation, based on individual assessment, to clinically vulnerable individuals including those with cerebral palsy, learning disabilities, multiple sclerosis and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.
Diabetes	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.
Immunosuppression (see contraindications and precautions section on live attenuated influenza vaccine)	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, bone marrow transplant, HIV infection at all stages, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement disorder) 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. It is difficult to define at what level of immunosuppression a patient could be considered to be at a greater risk of the serious consequences of influenza and should be offered influenza vaccination. This decision is best made on an individual basis and left to the patient's clinician. 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 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

Other groups

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. Vaccination should also be offered to household contacts of immunocompromised individuals, i.e. 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 two 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 dosage 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 SPCs.

Children aged two to less than seventeen years old NOT IN clinical risk groups

Starting from September 2013, an extension of the programme to all children aged two to less than seventeen years old is being phased in from the youngest age groups. 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 six months to less than two 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 four weeks later. The inactivated influenza vaccines are interchangeable; the second dose, if required, should be given at least four weeks after the first dose in accordance with the manufacturer's SPC for that vaccine.

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

Children aged two years 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 two and less than nine years should be offered a second dose of LAIV at least four 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. The quadrivalent vaccine has both lineages of influenza B and may therefore provide better protection against the circulating B strain(s) than trivalent inactivated influenza vaccines. Children aged two to less than nine years old who have not received influenza vaccine previously should be offered a second dose of the vaccine at least four weeks later.

The inactivated influenza vaccines are interchangeable; the second dose, if required, should be given at least four weeks after the first dose in accordance with the manufacturer's SPC for that vaccine.

Table 19.5 summarises the advice on influenza vaccination for children

Preterm infants

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 six months of age.

Table 19.5 Influenza vaccination for children under 18 years old

Eligible cohort	Vaccine available: Children in clinical risk groups*	Vaccine available: Children not in clinical risk groups[1]
Six months to less than two years old	Offer suitable quadrivalent inactivated flu vaccine.	Not applicable.
Children aged two years to less than 18 years old[1]	Offer LAIV (Fluenz® Tetra) (unless medically contraindicated[2])	Offer LAIV (Fluenz® Tetra)

* Children in clinical risk groups aged six month to less than nine years who have not received flu vaccine before should be offered two doses of the appropriate flu vaccine (given at least four weeks apart).

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.

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. Whilst there is no evidence of risk with LAIV (Toback *et al*., 2012), inactivated influenza vaccines are preferred for those who are pregnant. There is no need, however, to specifically test eligible girls for pregnancy or to advise avoidance of pregnancy in those who have been recently vaccinated.

Contraindications

The SPCs 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 screening and immunisation team in the NHS England team, a consultant in communicable disease control or a consultant paediatrician, 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; HIV infection not on highly active antiretroviral therapy (HAART); cellular immune deficiencies; and high dose corticosteroids. It is not contraindicated for use in children or adolescents with stable HIV infection receiving antiretroviral therapy; or who are receiving topical corticosteroids, inhaled corticosteroids or low-dose systemic corticosteroids, or those receiving corticosteroids as replacement therapy, e.g. 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 SPC for Fluenz® Tetra.

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.

Immunosuppression and HIV infection

Individuals who have immunosuppression and HIV infection (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, i.e. 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 Fluenz® Tetra to immunocompromised contacts for one to two weeks following vaccination. In the US, where there has been extensive use of the LAIV, there have been no reported instances of illness or infections from the vaccine virus among immunocompromised patients inadvertently exposed. Where close contact with very severely immunocompromised patients (e.g. bone marrow transplant patients requiring isolation) is likely or unavoidable (for example, household members), however, 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 nine 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 (Fluenz® Tetra), 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 will be published prior to the influenza season.[1]

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 LAIV in the hospital setting. LAIV remains the preferred vaccine for this group and the intranasal route is less likely to cause systemic reactions.

Children with egg allergy but who also have another condition which contraindicates LAIV should be offered 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 nine years who have not been previously vaccinated against influenza will require a second dose (of either LAIV or inactivated vaccine as appropriate).

Adult patients 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 for 0.5 ml dose), excepting those with severe anaphylaxis to egg which has previously required intensive care who should be referred to a specialist for assessment with regard to receiving immunisation in hospital.

Egg-allergic adults and children over age nine years with egg allergy can also be given the quadrivalent inactivated egg-free vaccine, Flucelvax® TETRA, which is licensed for use in this age group.

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 two weeks of administration of LAIV may adversely affect the effectiveness of the vaccine.

1 https://www.gov.uk/government/publications/ influenza-vaccine-ovalbumin-content

Exposure of healthcare professionals to live attenuated influenza vaccine 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 four 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 one to two days without treatment. Nasal congestion/ rhinorrhoea, reduced appetite, weakness and headache are common adverse reaction 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 five 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 following influenza vaccines should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card scheme at http://yellowcard.mhra.gov.uk/

The quadrivalent cell cultured inactivated influenza vaccine (QIVc), quadrivalent inactivated influenza vaccine (QIV) and high-dose trivalent inactivated influenza vaccine (TIV-HD) carry a black triangle symbol (▼). This 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.

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 five years of age in other countries. The SPC for Enzira® also indicates that a high rate of fever was reported in the age group aged five to under nine years. Due to the risk of febrile convulsions, the indication for Enzira® is restricted to use in adults and children aged five years and older. This vaccine will not be part of the central supply for use in children, and is no longer available for purchase by the practice.

There remains no evidence that other trivalent 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 at:

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 four UK countries – see respective websites for details. LAIV is purchased centrally for eligible children aged two to less than 18 years. For eligible children under 18 years of age where LAIV is medically contraindicated, a suitable inactivated quadrivalent vaccine will be supplied. 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

Mylan (BGP Products), formerly Abbott Healthcare 0800 358 7468
AstraZeneca UK Ltd 0845 139 0000
GlaxoSmithKline 0800 221 441
MASTA 0113 238 7552

Sanofi Pasteur 0845 023 0440
Seqirus UK Ltd 08457 451500

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).

References

Advisory Committee on Immunization Practices (ACIP) Special Situations, General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP) Feb 27th 2018. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html

Allison MA Daley MF, Crane LA *et al*. (2006) Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003-2004 season. *J Pediatr* **149**: 755-62.

Ambrose CS, Levin MJ, Belshe RB. The relative efficacy of trivalent live attenuated and inactivated vaccines in children and adults. *Influenza And Other Respiratory Viruses* 2011;5:67-75.

American Academy of Pediatrics (2003) Active immunization. In: Pickering LK (ed.) *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th edition. Elk Grove Village, IL: American Academy of Pediatrics, p. 33.

Ampofo K, Gesteland PH, Bender J *et al*. (2006) Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. *Pediatrics* **118**(6):2409-17.

Ashkenazi S, Vertruyen A, Aristegui J. *et al*. (2006) Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. *Pediatr Infect Dis J* 25(10): 870-9. **http://www.ncbi.nlm.nih.gov/sites/entrez/17006279**

Ashkenazi S, Vertruyen A., Aristegui, J. *et al.* [2006] Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. *Pediatr Infect Dis J* 870-9.

Barker WH and Mullooly JP (1982) Pneumonia and influenza deaths during epidemics. *Arch Int Med* **142**: 85–9.

Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, *et al.* Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis*. 2016;16(8):942-51. https://doi.org/10.1016/S1473-3099(16)00129-8 PMID: 27061888

Belshe RB, Edwards KM, Vesikari T *et al*. (2007) Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med* 356(7): 685-96. http://www.ncbi.nlm.nih.gov/sites/entrez/17301299

Benowitz I, Esposito DB, Gracey KD *et al*. (2010) Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis*. 51: 1355- 61.

Block S L, Toback SL, Yi T *et al*. (2009) Efficacy of a single dose of live attenuated influenza vaccine in previously unvaccinated children: a post hoc analysis of three studies of children aged 2 to 6 years. *Clin Ther*. **31**: 2140-7.

Bracco Neto H, Farhat CK, Tregnaghi MW, *et al*. (2009) Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. *Pediatr Infect Dis J*. **28**: 365-71

British HIV Association (2015) guidelines on the use of vaccines in HIV-positive adults: http://www.bhiva.org/documents/Guidelines/Vaccination/2015-Vaccination-Guidelines.pdf

Bryan P and Seabroke S (2011) No increased risk of febrile convulsions after seasonal influenza immunisation in UK. *Lancet* **377**: 904.

Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2013–2014 September 20, 2013 / 62(RR07);1- 43 http://www.cdc.gov/mmwr/preview/mmwrhtml/ rr6207a1.htm?s_cid=rr6207a1_w#LiveAttenuatedInfluenzaVaccineshttp://

www.cdc.gov/mmwr/preview/mmwrhtml/rr6207a1.htm?s_cid=rr6207a1_w#LiveAttenuatedInfluenzaVaccines

Centers for Disease Control and Prevention (2012) Persons Who Should Not Be Vaccinated Influenza Prevention and Control Recommendations. http://www.cdc.gov/flu/professionals/acip/shouldnot.htm

Coffin SE, Zaoutis TE, Rosenquist AB *et al*. (2007) Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza. *Pediatrics* **119**(4):740-8.

Committee on Safety of Medicines (2003) Further data support safety of thiomersal in vaccines. Available from: www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/

Product-specificinformationandadvice/accinesafetyThiomersal(ethylmercury) containingvaccines/index.htm

Accessed: May 2010

Department of Health (2013) Health Technical Memorandum 07-01: Safe management of healthcare waste. https://www.gov.uk/government/uploads/system/uploads/ attachment_data/file/167976/HTM_07-01_Final.pdf

Accessed March 2014.

Des Roches A, Paradis L, Gagnon R, *et al.* (2012). Egg-allergic patients can be safely vaccinated against influenza. *J Allergy Clin Immunol.* **130**(5):1213-6.

Dexter LJ, Teare MD, Dexter M *et al*. (2012) Strategies to increase influenza vaccination rates: outcomes of a nationwide cross-sectional survey of UK general practice. *BMJ Open*. **2**:e000851.

Domnich A, Arata L, Amicizia D *et al*. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. *Vaccine* 35 (2017) 513–520

DiazGranados CA, Dunning AJ, Kimmel M *et al*. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. N Engl J Med. 2014;**371**(7):635-645

Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, et al. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. New England Journal of Medicine. 2017;**376**(25):2427-36

Eick AA, Uyeki TM, Klimov A *et al*. (2010) Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med*. **165**: 104-11.

European Medicines Agency/ Committee for Medicinal Products for Human Use (CHMP) Guideline on Influenza Vaccines (2016) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211324.pdf Accessed November 22, 2017

Fezeu L, Julia C, Henegar A, Bitu J *et al*. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta- analysis Obes Rev. 2011 Aug;12(8):653-9.

Fleming DM, Watson JM, Nicholas S *et al*. (1995) Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989/90 using a general practice database. *Epidemiol Infect* **115**: 581–9.

Fleming DM, Crovari P, Wahn U *et al*. (2006) Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J* **25**(10): 860-9. http://www.ncbi.nlm.nih.gov/sites/entrez/17006278

Goddard NL, Kyncl J and Watson JM (2003) Appropriateness of thresholds currently used to describe influenza activity in England. *Common Dis Public Health* **6**: 238–45.

Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*. 2006 Feb 20;24(8):1159-69. Epub 2005 Sep 19.

Gravenstein S, Davidson HE, Taljaard M *et al*. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017 Sep;**5**(9):738-746

Haralambieva IH, Painter SD, Kennedy RB, Ovsyannikova IG, Lambert ND, Goergen KM, *et al*. (2015) The Impact of Immunosenescence on Humoral Immune Response Variation after Influenza A/H1N1 Vaccination in Older Subjects. *PLoS ONE* 10(3): e0122282. doi:10.1371/journal.pone.0122282

Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus by age group in England and Wales 1999–2010. *Influenza and Other Respiratory Viruses* 2013; 7(1), 35–45.

Heinonen OP, Shapiro S, Monson RR *et al*. (1973) Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* **2**: 229–35.

Heinonen S, Silvennoinen H, Lehtinen P *et al.* (2011) Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: an observational cohort study. *Lancet Infect Dis* **11**(1): 23-9.

Hoft DF, Babusis E, Worku S, *et al.* Live and inactivated influenza vaccines induce similar humoral responses, but only live vaccines induce diverse T-cell responses in young children. J Infect Dis 2011;204:845–53.

Hurwitz ES, Schonberger LG, Nelson DB *et al*. (1981) Guillain-Barré syndrome and the 1978-1979 influenza vaccine. *N Eng J Med* **304**(26):1557-61.

Izurieta HS, Chillarige Y,Kelman J *et al.* Relative Effectiveness of Influenza Vaccines. JID 2018 doi: 10.1093/infdis/jiy716. [Epub ahead of print].

Jamieson D, Honein MA, Rasmussen SA *et al*. (2009) H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* **374**: 451-8.

The Joint Committee for Vaccination and Immunisation statement on the annual influenza vaccination programme – extension of the programme to children 25 July 2012 Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/ 224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012. pdf

Joint Committee on Vaccination and Immunisation Minutes of the February 2015 meeting. Available at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and- immunisation#minutes

Joint Committee on Vaccination and Immunisation. Statement on the use of nasal spray flu vaccine for the childhood influenza immunisation programme. August 2016. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/548515/JCVI_statement.pdf

Joint Committee on Vaccination and Immunisation Minutes of the June 2017 meeting. Available at : https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes

Joint Committee on Vaccination and Immunisation Minutes of the October 2017 meeting. Available at : https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes

Joint Committee on Vaccination and Immunisation Minutes of the October 2018 meeting. Available at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes

Kaplan JE, Katona P, Hurwitz ES *et al*. (1982) Guillain-Barré syndrome in the United States, 1979-80 and 1980-81. *JAMA* **248**(6):698-700

Lang P-O, Mendes A, Socquet J, Assir N, Govind S, Aspinall R. Effectiveness of influenza vaccine in aging and older adults: comprehensive analysis of the evidence. *Clinical Interventions in Aging*. 2012;7:55-64. doi:10.2147/CIA.S25215.

Lasky T, Terracciano GJ, Magder L *et al*. (1998) The Guillain-Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med* **339**: 1797–1802.

Lau LLH, Cowling BJ, Fang VJ *et al*. (2010) Viral shedding and clinical illness in naturally acquired influenza virus infections. *J Infect Dis* **201**: 1509-16.

Mangtani P, Cumberland P, Hodgson CR *et al*. (2004) A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *J Infect Dis* **190**(1): 1–10

Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the U.K. J Med Econ. 2015;**18**(9):746-61.

McNeil SA, Dodds, LA, Fell, DB *et al*. Effect of respiratory hospitalization during pregnancy on infant outcomes. *Am J Obstet Gynecol* 204: [6 Suppl 1.] S54-7, Epub 2011 Apr 24. 2011 Jun.

Mendez-Figueroa H, Raker, C and Anderson, BL. Neonatal characteristics and outcomes of pregnancies complicated by influenza infection during the 2009 pandemic. *Am J Obstet Gynecol* 204. 204: [6 Suppl 1.] S58-63, Epub 2011 Mar 31. 2011 Jun.

Miller E, Andrews N, Stellitano L, *et al*. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. BMJ 2013;346: f794.

Morgan OW, Bramley A, Fowlkes A, *et al*. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease *PLoS One*. 2010 Mar 15;5(3):

Neuzil KM, Reed, GW, Mitchel, EF *et al*. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 148: [11.] 1094-102. 1998 Dec 1.

Neuzil KM, Jackson LA, Nelson J *et al*. (2006) Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naive 5-8-year-old children. *J Infect Dis* **194**(8): 1032-9. http://www.ncbi.nlm.nih.gov/sites/entrez/16991077

Nicoll A, Ciancio B, Tsolova S *et al*. (2008) The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. *Euro Surveill* **13**(43). pii: 19018.

Nohynek H, Jokinen J, Partinen M, *et al*. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One 2012; 7: e33536.

O'Brien MA, Uyeki TM, Shay DK *et al*. (2004) Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics* **113**(3 Pt 1):585-93.

Omer SB, Goodman, D, Steinhoff, MC *et al*. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. *PLoS Med*. 8: [5.] e1000441 Epub 2011 May 31. 2011 May.

Osterholm, MT, Kelley, NS, Sommer, A and Belongia, EA (2012) Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 12. (1.), 36-44.

Partinen M, Saarenpaa-Heikkila O, Ilveskoski I, *et al*. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. PLoS One 2012; 7: e33723.

Pebody R *et al*. Pandemic influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. *Eurosurveillance* 2010 **15**(20): 19571.

Pebody R, Warburton F, Ellis J *et al*. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Eurosurveillance*. 2016;21(38):pii=30348. https://doi.org/10.2807/1560-7917.ES.2016.21.38.30348

Pebody R, Green H, Andrews N *et al*. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. *Eurosurveillance.* 2015;20(39):pii=30029. https://doi.org/10.2807/1560-7917.ES.2015.20.39.30029

Pebody R, Warburton F, Ellis J *et al*. End-of-season influenza vaccine effectiveness in adults and children, United Kingdom, 2016/17. *Eurosurveillance* 2017, 22, 17-00306 (2017), https://doi.org/10.2807/1560-7917.ES.2017.22.44.17-00306

Pebody RG, Zambon M, Ramsay M. Flu vaccines: an annual challenge. BMJ. 2018 Jun 27;361:k2705. doi: 10.1136/ bmj.k2705. PubMed PMID: 29950432.

Pierce M, Kurinczuk, JJ, Spark, P *et al*. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ*. 342. 342:d3214. doi: 10.1136/bmj.d3214.: d3214. 2011 2011 Jun 14.

Poehling KA, Edwards KM, Weinberg GA *et al*. (2006) The underrecognized burden of influenza in young children. *N Engl J Med* **355**(1):31-40.

Poehling KA, Szilagyi, PG, Staat, MA *et al*. (2011) Impact of maternal immunization on influenza hospitalizations in infants. *Am J Obstet Gynecol* 204: [6 Suppl 1.] S141-8. Epub Feb 23. 2011 Jun.

Presanis AM, Pebody RG, Paterson BJ *et al*. Changes in severity of 2009 pandemic A/ H1N1 in England: A Bayesian evidence synthesis. *BMJ*. **343**:d5408 doi:10.1136/bmj. d5408. 2011 Sept 8.

Ritzwoller DP, Bridges CB, Shetterly S *et al*. (2005) Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. *Pediatrics* **116**: 153-9.

Roscelli JD, Bass JW, Pang L (1991) Guillain-Barré syndrome and influenza vaccination in the US Army 1980-1988. *Am J Epidemiol* **133**(9):952-5.

Shuler CM, Iwamoto M, Bridges CB, *et al*. (2007) Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003- 2004.

Pediatrics **119**: e587-95.

Stowe J, Andrews N, Wise L and Miller E (2009) Investigation of the temporal association of Guillain-Barré Syndrome with influenza vaccine and influenza-like illness using the United Kingdom General Practice Research Database. *Am J Epidemiol* **169**(3):382-8.

Stowe J, Andrews N, Bryan P, *et al*. (2011) Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study. *Vaccine* 29, 9467-72.

Subbramanian RA, Basha S, Shata MT, *et al.*. Pandemic and seasonal H1N1 influenza hemagglutinin-specific T cell responses elicited by seasonal influenza vaccination. *Vaccine* 2010;28:8258–67.

Tamma PD, Ault KA, del Rio C, Steinhoff MC *et al*. (2009) Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* **201**(6): 547-52.

Therapeutic Goods Administration Australian Government (2010) Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-100702.htm

Thommes EW, Ismaila A, Chit A, Meier G, Bauch CT. Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom. BMC Infect Dis. 2015 Oct 27;**15**:465

Thompson WW, Price C, Goodson B *et al*. (2007) Early thiomersal exposure and neuropsychological outcomes at 7 to 10 years. *N Eng J Med* **357**:1281-92.

Thompson WW, Shay DK, Weintraub E *et al*. (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* **289**(2):179-86.

Thompson WW, Shay DK, Weintraub E *et al*. (2004) Influenza-associated hospitalizations in the United States. *JAMA* **292**(11):1333-40.

Thorrington D, van Leeuwin E, Ramsay M *et al.* BMC Medicine (2017) **15:**166 . DOI 10.1186/s12916-017-0932-3

Toback SL, Beigi R, Tennis P *et al*. (2012). Maternal outcomes among pregnant women receiving live attenuated influenza vaccine. *Influenza Other Respi Viruses* **6**, 44-51.

Van Buynder PG, Konrad S, Van Buynder JL *et al*.The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine*. 2013 Dec 9;31(51):6122-8. doi: 10.1016/j.vaccine.2013.07.059. Epub 2013 Aug 6.

Van Kerkhove MD, WHO Working Group for Risk Factors for Severe H1N1pdm Infection. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global

pooled analysis. PLoS Med. 2011 Jul;8(7):e1001053.

Wilde JA, McMillan JA, Serwint J *et al*. (1999) Effectiveness of influenza vaccine in health care professionals: a randomised trial. *JAMA* **281**: 908–13.

Wright PF, Thompson J, Vaughn WK *et al*. (1977) Trials of influenza A/New Jersey/76 virus vaccine in normal children: an overview of age-related antigenicity and reactogenicity. *J Infect Dis* **136** (suppl): S731–41.

Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* **362**: 1708-19.

Zaman K, Roy E , Arifeen SE *et al* (2008) Effectiveness of maternal influenza immunisation in mothers and infants. *N Engl J Med* **359**: 1555-64.

Zhou H, Thompson WW, Viboud CG *et al*. (2012) Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. *Clin Infect Dis* **54**: 1427-36.