



The Vaccines

In general, seasonal influenza vaccines are trivalent, containing a mixture of influenza A and B strains thought most likely to circulate in the coming season. However, monovalent vaccines have been produced against candidate pandemic strains. It is now common practice to use reassortant strains for production that give high yields of the appropriate surface antigens. Reassortant strains for vaccine production have the surface glycoproteins (HA and NA) of the circulating epidemic virus but the internal proteins of a standardized production strain, eliminating much of the risks associated with handling pathogenic strains. The virus is grown in chick embryos or cell cultures for the production of vaccines.

In 2009 monovalent Pandemic influenza vaccines were developed to vaccinate persons against the 2009 H1N1 pandemic. These vaccines are no longer in use since 2011. In this information sheet, inactivated influenza vaccine generally refers to seasonal, Trivalent Inactivated Influenza Vaccine (TIV).

Inactivated vaccine

The inactivated vaccine is made from highly purified, egg-grown viruses. There are three types of inactivated vaccines - whole virus vaccines, split virus and subunit vaccines. Inactivated seasonal vaccines are conventionally subunit or split virion vaccines. Split virus preparation contains viruses that have been treated with an organic solvent to remove surface glycoproteins and thus reduce vaccine reactogenicity. Influenza vaccine contains 15 µg of each antigen per 0.5 ml dose of the three virus strains (usually two type A and one type B) that are likely to circulate during the upcoming influenza season (CDC, 1999).

Due to the high mutation rate of the virus a particular vaccine formulation is effective for at most about a year. Therefore, three strains are chosen for selection in that year's flu vaccination by the WHO Global Influenza Surveillance Network. In February, the World Health Organization (WHO) makes recommendations concerning the virus strains to be included in vaccine production for the forthcoming winter in the Northern Hemisphere. A second recommendation is made in September which relates to vaccines to be used for the winter in the Southern Hemisphere (WER, 1999). These recommendations are based on information collected from more than 100 laboratories worldwide that conduct influenza surveillance. All the vaccines are comparable because of similar composition and production methods.

Antibiotics including neomycin, gentamicin, kanamycin or polymyxin may be used in production of the vaccine along with sodium bisulfite. All manufacturers use thiomersal or formaldehyde as a preservative and some use gelatine as a stabilizer. In addition, the vaccines contain low levels of residual egg proteins.

Intranasal influenza vaccine

The Intranasal influenza vaccine is a live attenuated and cold adapted vaccine. Like the injectable vaccine the intranasal vaccine is grown in egg culture and may contain residual egg proteins. Intranasal influenza vaccines were first licensed for use in some countries in 2003 and have been widely used in these countries. The vaccine virus has been shown to replicate in the nasal secretions of vaccinated individuals, however, transmission rates to unvaccinated individuals have shown to be low (Vesikari T et al., 2006). Live, attenuated influenza vaccine (LAIV) can be used for healthy non-pregnant persons aged 2 - 49 years. Available data do not indicate that influenza vaccine causes fetal harm when administered to a pregnant woman (CDC 2010).

Its safety has not been established for individuals with underlying medical conditions that confer a higher risk for influenza complications. (CDC, 2012).

Adverse events - Inactivated influenza vaccine

In general, influenza vaccines are well tolerated (France et al., 2004; Hambridge et al., 2006; Greene et al., 2010). However, in contrast to vaccine against other diseases, the annual reformulation of the influenza vaccine may be more frequently associated with unexpected adverse reactions (e.g. GBS in 1976, fever in Europe in 1995, Ocular Respiratory Syndrome in Canada in 2000, convulsion in Australia in 2010).

Mild adverse events

Local reactions

In placebo-controlled blinded studies, the most frequent side-effect of influenza vaccination is soreness at the vaccination site (affecting 10–64% of vaccinees); which lasts up to two days (Govaert et al., 1993; Margolis et al., 1990). These reactions are generally mild and transient and resolve spontaneously within two to three days and further medical attention is not required. Analysis by gender of 14 studies has revealed that females (both young and elderly) report significantly more local reactions (Beyer, 1996). Several studies have shown a greater frequency of local reactions of whole cell, adjuvanted and intradermal vaccines compared to split virus vaccine and subunit vaccines (Beyer et al., 1998). Local reactions are also more frequent with vaccines that contain a "high" HA antigen content compared to low those that contain a "low" HA antigen content. Vaccines with 180 mcg of HA antigen resulted in solicited local reactions in 36 per 100 vaccinees compared with a standard dose of 45 mcg was associated with 24 per 100 vaccinees (Falsey et al., 2009).

Systemic reactions

Individuals without previous exposure to the vaccine antigens, such as children, may show fever, general discomfort and muscle pain (Barry et al., 1976). These reactions occur within 6–12 hours of vaccination and generally persist 1–2 days (CDC, 1999). Fever was noted among 12 per 100 children aged 1–5 years, 5 per 100 aged 6–15 years (Neuzil et al., 2001). In adults the rate of these events is similar after TIV and placebo. (Fiore A et al 2010).

No increased risk of febrile seizures following vaccination was observed in children 6–23 months (Hambridge et al., 2006; Greene et al., 2010; Stowe et al., 2011). As a singular event, in 2010, preliminary data showed an elevated risk of up to 1 case per 100 for febrile reaction to one trivalent flu vaccine among children less than three years in Australia (Kelly et al., 2011). The Committee of the Institute of Medicine (2011) stated a moderate degree of confidence in the epidemiologic evidence based on 4 studies consistently reporting a null association (France et al., 2004; Goodman et al., 2006; Greene et al., 2010; Hambridge et al., 2006).

Among older persons and healthy young adults, placebo-controlled trials demonstrated that administration of inactivated influenza vaccine is not associated with higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (Bridges et al., 2000; Cates et al., 2008; Govaert et al., 1993; Margolis et al., 1990; Nichol et al., 1996). Systemic adverse events among persons aged ≥ 65 years were more frequent after vaccination with a vaccine containing a high dose of 180 mcg of HA antigen (36 per 100 vaccinees) compared with a standard dose of 45 mcg (24 per 100 vaccinees). Typically, reactions were mild and transient, resolving within 3 days in the majority of subjects. (Falsey et al., 2009).

Severe adverse events

Anaphylaxis

Based on a controlled study (Greene et al., 2010) that lacked validity and precision to assess an association between influenza vaccine and anaphylaxis, the Committee of the Institute of Medicine (2011) has limited confidence in the epidemiologic evidence, however, based in mechanistic evidence including 22 cases presenting temporality and clinical symptoms consistent with anaphylaxis sees a causal relationship between influenza and anaphylaxis.

Immediate – presumably allergic – reactions (e.g. hives, angioedema, wheeze and anaphylaxis) occur rarely after influenza vaccination (Bierman et al., 1997; Nakayama et al., 2007; Vellozzi et al., 2009).

Guillain-Barré syndrome

The 1976 swine influenza vaccine was associated with an increased risk of GBS (Hurwitz et al., 1981). Among those who received this vaccine, the rate of GBS that exceeded the background rate was slightly less than 10 cases per million vaccinated (CDC, 1998). The risk of GBS associated with subsequent influenza vaccines (prepared from different virus strains) is less clear. It is difficult to detect a small increase in risk for a rare disease such as GBS. The annual incidence rate of GBS is approximately 10–20 cases per million adults (CDC, 2010). In four influenza seasons studied between 1977 and 1991, the relative risk of GBS following influenza vaccination was not statistically significant in any of the studies (Kaplan et al., 1982; Hurwitz et al., 1981). However there was a small excess risk of GBS in vaccine recipients aged 18 to 64 years in the 1990/91 vaccine season in the United States (CDC, 1993). In a population based study the estimated relative incidence of GBS during the primary risk interval (weeks 2 through 7) compared with the control interval (weeks 20 through 43) was 1.45 (95% confidence interval, 1.05 - 1.99; $P = .02$). This study concluded that Influenza vaccination is associated with a small but significantly increased risk for hospitalization because of GBS (Juurlink et al., 2006). The estimated risk of one to two cases per million vaccinated is less than that for severe influenza (Lasky et al., 1998). Sivadon-Tardy et al. (2009) identified serologically confirmed influenza virus infection as a trigger of GBS, with time from onset of influenza illness to GBS of 3 - 30 days. Influenza-related GBS was four to seven times more frequent than influenza-vaccine-associated GBS.

The Committee of the Institute of Medicine (2011) stated a moderate degree of confidence in nine controlled studies (Burwen et al., 2010; Greene et al., 2010; Hughes et al., 2006; Hurwitz et al., 1981; Juurlink et al., 2006; Kaplan et al., 1982; Roscelli et al., 1991; Stowe et al., 2009; Tam et al., 2007), that did not support that influenza vaccination is associated with GBS. While the weight of epidemiologic evidence does not support a causal link between influenza vaccinations evaluated over the last 30 years, the committee found that an association cannot be confidently ruled out, particularly for future vaccine strains and therefore concluded the evidence to be inadequate to accept or reject a causal relationship between influenza vaccine and GBS.

Oculo-respiratory syndrome (ORS)

Oculo-respiratory syndrome (ORS) has been characterized by an array of symptoms including bilateral red eyes, cough, wheeze, chest tightness, difficulty breathing, sore throat and difficulty swallowing, or facial swelling, occurring within 2 to 24 hours of influenza vaccination and generally resolving within 48 hours of symptom onset (Skowronski et al., 2003). Symptoms are typically mild and resolve quickly without specific treatment (National Advisory Committee on Immunization 2001, CDC 2010). ORS was first described following use of influenza vaccine in Canada and has been linked to higher proportions of micro-aggregates of unsplit virions in the vaccine. Although, initially passive surveillance demonstrated that nearly all cases were linked to vaccine from a single manufacturer cases have been reported at a much lower frequency with all types of killed influenza vaccine used in Canada (Public Health Agency of Canada 2005). The pathogenesis of ORS is unknown and is not thought to be directly due to vaccine type I hypersensitivity. Reported cases of ORS peaked in Canada with the 2000-2001 seasonal vaccine with rates reducing significantly in subsequent years (De Serres et al., 2005). Based on four controlled studies (De Serres et al., 2004; Hambridge et al., 2006; Scheifele et al., 2003; Skowronski et al., 2003) and taking into account mechanistic evidence, the Committee of the Institute of Medicine (2011) has a moderate degree of confidence in evidence suggesting an increased risk of a causal relationship between ORS and two particular vaccines used in three particular years in Canada.

Adverse events - Live attenuated influenza vaccine (LAIV)

LAIV contains live attenuated influenza viruses that have the potential to cause mild signs or symptoms related to vaccine virus infection. e.g., rhinorrhoea, nasal congestion, fever, or sore throat (CDC 2010).

Runny nose or nasal congestion (59 - 63 per 100), cough (28 per 100), fever (16 - 31 per 100) and decreased activity (16 - 23 per 100) has been noted after the first dose of intranasal vaccine (Piedra P et al., 2002, Tam et al., 2007, Vesikari T et al., 2007). The odds of having any symptom after the first dose of the intranasal vaccine compared with placebo (between days 0 and 10) is 1.56 (OR 1.24 - 1.97) (Piedra P et al., 2002). These symptoms do not tend to recur or are less frequent with the second dose or with vaccination in subsequent years (Piedra P et al., 2002, Vesikari T et al., 2002). In addition to this, other mild symptoms such as vomiting (10 per 100 vaccine vs. 2 per 100 placebo recipients), abdominal pain (4 per 100 vaccine vs. 0 placebo recipients) and muscle aches (14 per 100 vaccine vs. 2 per 100 placebo recipients) are reported at a higher rate than placebo. These symptoms tend to worsen between days 2 and 4 post vaccination and may last for up to 6 days.

Severe adverse events

Wheezing episodes with live attenuated influenza vaccine and asthma exacerbation or reactive airway disease episodes.

The Committee of the Institute of Medicine (2011) reviewed four studies to evaluate the risk of asthma or reactive airway disease episodes in children younger than 5 years of age (Belshe et al., 2004; Bergen et al., 2004; Gaglani et al., 2008; Piedra et al., 2005), and two additional controlled studies that compared LAIV to TIV (Ashkenazi et al., 2006; Belshe et al., 2007). Based on these studies, the committee stated a moderate degree of confidence in the epidemiologic evidence reporting a null association. Data published since the committee's report has also shown that no excess risk in asthmatic children 2 years and older (Ambrose et al., 2012). While the weight of epidemiologic evidence does not support a causal link, the committee found that an evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age. For children 5 years of age or older, the committee showed similarly a moderate degree of confidence in the epidemiologic evidence, based on four papers consistently reporting a null association (Belshe et al., 2004; Bergen et al., 2004; Gaglani et al., 2008; Piedra et al., 2005) and one additional controlled study that compared LAIV to TIV (Fleming et al., 2006). Again, while the weight of epidemiologic evidence does not support a causal link, the committee found that an evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children older than 5 years of age.

Anaphylaxis

Post marketing surveillance data has been reported from VAERS for live attenuated influenza vaccine which was licensed for use in 2003. Izurieta et al., 2005 reported that an estimated 2.5 million doses had been used in individuals 5 to 49 years of age. Their report included 7 reports of anaphylaxis which provides an estimated rate of anaphylaxis of 1 per 500,000 doses.

Severe neurological events

Severe neurological events reported included 2 cases of Guillain-Barré syndrome and 1 report of Bell's palsy. Passive surveillance is unable to determine if these events were causal or coincidental to vaccine administration. The Committee of the Institute of Medicine (2011), based on two controlled studies (Greene et al., 2010; Stowe et al., 2006), favoured a rejection of a causal relationship between inactivated influenza vaccine and Bell's palsy.

Other safety issues

Persons with Chronic Medical Conditions

Several studies have found no increase in asthma exacerbations/wheezing among children or adults after TIV (American Lung Association Asthma Clinical Research Centers 2001; Kramarz et al, 2001; Hak et al, 2005). Groothuis et al. (1994) reported that 20 to 28 per 100 children between 9 months and 18 years of age suffering from asthma had injection-site pain and swelling at the site of influenza vaccination. Daubeney et al. (1997), found injection-site reactions among 23 per 100 children between 6 months and 4 years suffering from chronic heart or lung disease. In one study injection-site reactions did not differ among 53 children aged 6 months – 6 years with high-risk medical conditions and 305 healthy children aged 3 – 12 years (Wright et al., 1977).

Of two studies that had no placebo comparison group, one study looking at children with high-risk medical conditions of 52 children aged 6 months – 3 years found fever among 27 per 100 children and irritability and insomnia among 25 per 100 children (Gonzalez et al., 2000). The other study included 33 children aged 6 – 18 months of which one child developed irritability and one with fever and seizures following immunization (Groothuis, 1991).

Immunocompromised Persons

Data demonstrating safety of inactivated influenza vaccine for HIV-infected persons are limited, but no evidence exists that vaccination has a clinically important impact on HIV infection or immunocompetence. No substantial increase in the replication of HIV was found in recent studies (Glesby et al., 1996; Fowke et al., 1997; Fuller et al., 1999), nor were CD4+ T-lymphocyte cell counts reduced after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons (Staprans et al., 1995; Sullivan et al., 2000).

Pregnant women and neonates

TIV is recommended for pregnant women at any stage of pregnancy. Inactivated vaccines are recommended for vaccination programs for children 6 months – two years old. In children older than 2 years, either inactivated vaccine (IV) or live-attenuated vaccine (LAIV) is an appropriate choice for vaccination programs (SAGE 2012).

Available data do not indicate that inactivated influenza vaccine causes fetal harm when administered to pregnant women. During 2000 – 2003, among pregnant women receiving TIV, 10 per 1,000,000 adverse events were reported to the US Vaccine Adverse Event Reporting System (VAERS). Among these events injection-site reactions occurred in 4.5 and systemic reactions (e.g., fever,

headache, and myalgias) in 8 per 1,000,000 women receiving vaccines. In addition, 1.5 miscarriages were reported per 1,000,000, however, were not known to be related causally to vaccination (Sumaya et al., 1979; Deinart et al., 1981; Englund et al., 1993; Pool et al., 2006; CDC, 2010). An international review of data also concluded that no evidence suggests harm to the fetus (Mak et al., 2008). In a randomized controlled trial in Bangladesh, and no severe adverse events were reported in any study group (Zaman et al., 2008). However safety data actively collected during the first trimester of pregnancy are still limited (Skowronski et al., 2009)

Asthma and immediate respiratory symptoms

Concern has been expressed that inactivated vaccine might exacerbate asthma. This has not been proven, although recent studies (Park, 1998; Nicholson, 1998; Reid, 1998) suggested there might be a small risk. The live attenuated cold adapted trivalent vaccine has also not been shown to exacerbate asthma when given to children with existing asthma (Fleming et al., 2007; Gaglani et al., 2008). Immediate respiratory symptoms after vaccination represents coincidental illness unrelated to influenza vaccine (CDC, 2010).

Simultaneous administration of other vaccines, including childhood vaccines

The target groups for influenza and pneumococcal vaccination overlap considerably. For persons at high risk who have not previously been vaccinated with the 23 valent pneumococcal vaccine, health care providers should strongly consider administering pneumococcal and influenza vaccines concurrently. Both vaccines can be administered at the same time at different sites without increasing side-effects (Grilli et al., 1997; Fletcher et al., 1997). However, influenza vaccine is administered each year, whereas the 23 valent pneumococcal vaccine is generally administered once only. Children at high risk of influenza-related complications can receive influenza vaccine at the same time they receive other routine vaccinations, including pertussis vaccine and using, if possible, DTaP which is less frequently associated with fever.

Egg and thiomersal allergy

When considering vaccination in a patient with a history of egg allergy, one should take into account the severity of the egg allergy, the egg content of vaccines, and the setting of vaccine administration. It seems that the risk of anaphylaxis to the influenza vaccine in patients with egg allergy may be much lower than previously thought. (Gruenberg and Shaker, 2011). Hypersensitivity to eggs has been listed as a contraindication to influenza vaccination where vaccine is prepared by inoculation of virus into chicken eggs. Several studies have indicated the safety of influenza vaccination of persons with egg allergy (James et al., 1998; Esposito et al., 2008; Chung et al., 2010; Owens et al., 2011; Webb et al., 2011; Howe et al., 2011), leading to reducing the contraindication in several package inserts to severe allergic reaction (e.g., anaphylaxis) to egg protein. Among studies in which the quantity of egg protein (ovalbumin) content of the administered vaccine was reported, up to 1.4 µg/mL (0.7 µg/0.5 mL dose) was tolerated without serious reactions (Owens et al., 2011; Webb et al., 2011; Howe et al., 2011).

Although exposure to vaccines containing thiomersal can lead to induction of hypersensitivity, most patients do not develop reactions when administered as a component of vaccines. When reported, hypersensitivity to thiomersal usually has consisted of local, delayed-type hypersensitivity reactions. However, immediate hypersensitivity reactions possibly due to the thiomersal contained in the influenza vaccine have also been reported (Lee-Wong M et al., 2005).

Other associations with no proven causal effect

Rarely, the following events have been temporally associated with immunization: vasculitis (Mader, 1993; Institute of Medicine, 2011), uveitis (Blanche, 1994), and delirium (Boutros, 1993), and cranial palsies. Furthermore associated were arthropathy, optic neuritis, polyarteritis nodosa, fibromyalgia, brachial neuritis, stroke (Institute of Medicine, 2011). No causal effect has, however, been demonstrated.

Summary of mild and severe adverse events – Inactivated influenza vaccine

Nature of Adverse event	Description	Rate/doses
Mild	<u>Local reactions</u> Injection site reactions	10 - 64 per 100
	<u>Generalized reactions</u> Fever in children 1 – 5 years of age	12 per 100
	Fever in children 6 – 15 years of age	5 per 100
Severe	Anaphylaxis	0.7 per 10 ⁶
	Guillain-Barré	1 – 2 per 10 ⁶
	Oculo-respiratory syndrome (events of moderate severity)	76 per 10 ⁶

Summary of mild and severe adverse events – Live attenuated influenza vaccine

Nature of Adverse event	Description	Rate/doses
Mild	<u>Local reactions</u>	
	Runny nose or nasal congestion	59 - 63 per 100
	Cough	28 per 100
	<u>Generalized reactions</u>	
	Fever	16 - 31 per 100
	Decreased activity	16 - 23 per 100
	Vomiting	10 per 100
Severe	Abdominal pain	4 per 100
	Muscle aches	14 per 100
	<u>Systemic reactions</u>	
	Wheeze in children of 6 - 11 months of age	14 per 100
	Anaphylaxis	1 per 500,000

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al., 2008, Institute of Medicine of the National Academies, 2011) and from data derived from a literature search on Pubmed in 2008 using key words "vaccine antigen", "Safety" and "adverse events". An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomized controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: http://www.who.int/vaccine_safety/vaccrates/en/index.html



**World Health
Organization**

Immunization, Vaccines and Biologicals Department
Quality, Safety & Standards
Global Vaccine Safety

vaccsafety@who.int

References

- Ambrose CS, Dubovsky F, Yi T, Belshe RB, Ashkenazi S (2012). The safety and efficacy of live attenuated influenza vaccine in young children with asthma or prior wheezing. *Eur J Clin Microbiol Infect Dis*. Mar 14.
- American Lung Association Asthma Clinical Research Centers. (2001). The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med*; 345:1529-36.
- Andrews N, Stowe J, Al-Shahi Salman R, Miller E (2011). Guillain-Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. *Vaccine*. 2011 Oct 19;29(45):7878-82. Epub 2011 Aug 27.
- Ashkenazi S, Vertruyen A, Aristegui J, Esposito S, McKeith DD, Klemola T, Bielek J, Kühn J, Bujnowski T, Desgrandchamps D, Cheng SM, Skinner J, Gruber WC, Forrest BD. (2006). CAIV-T Study Group. 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.
- Barry DW, Mayner RE, Hochstein HD, et al (1976). Comparative trial of influenza vaccines. II. Adverse reactions in children and adults. *American Journal of Epidemiology*, 104:47–59.
- Barry DW, Mayner RE, Staton E, et al. (1976). Comparative trial of influenza vaccines. I. Immunogenicity of whole virus and split product vaccines in man. *American Journal of Epidemiology*; 104:34–36.
- Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, Kemble G, Connor EM. (2007). CAIV-T Comparative Efficacy Study Group. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med*; 356(7):685-96.
- Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, Walker R, Hessel C, Cordova J, Mendelman PM. (2004). Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J*; 23(2):138-44.
- Beyer WE, Palache AM, Osterhaus AD. (1998) Comparison of Serology and Reactogenicity between Influenza Subunit Vaccines and Whole Virus or Split Vaccines: A Review and Meta-Analysis of the Literature. *Clin Drug Investig*;15(1):1-12.
- Beyer WEP, Palache AM, Kerstens R, Masurel N. (1996). Gender differences in local and systemic reactions of inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. *European Journal of Clinical Microbiology and Infectious Diseases*; 15:65–70.
- Bierman CW, Shapiro GG, Pierson WE, et al. (1997). Safety of influenza vaccine in allergic children. *Journal of Infectious Diseases*; 136:S652–S655
- Blanche P, Decrette C, Sicard D. (1994). Development of uveitis following vaccination for influenza. *Clinical Infectious Diseases*; 19:979.
- Boutros N, Keck BP. (1993). Delirium following influenza vaccination. *American Journal of Psychiatry*; 150:1899.
- Bridges CB, Thompson WW, Meltzer MI, et al. (2000). Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA*; 284:1655-63.
- Cates CJ, Jefferson TO, Rowe BH. (2008). Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev*:CD000364.
- CDC. (1993). Centers for Disease Control and Prevention. Prevention and control of influenza: Part 1, vaccines. *MMWR: Morbidity and Mortality Weekly Report*; 42(RR-6):1–14.
- CDC. (1998). Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR: Morbidity and Mortality Weekly Report*; 47(No.RR-6): 1-26.
- CDC. (1999). Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR: Morbidity and Mortality Weekly Report*; 48(No. RR-4): 1-28.
- CDC. (2010). Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR: Morbidity and Mortality Weekly Report*; 59(rr08);1-62.
- Daubeney P, Taylor CJ, McGaw J, et al. (1997). Immunogenicity and tolerability of a trivalent influenza subunit vaccine (Influvac) in high-risk children aged 6 months to 4 years. *Br J Clin Pract*; 51:87-90.
- De Serres G, Toth E, Ménard S, Grenier JL, Roussel R, Tremblay M, Douville Fradet M, Landry M, Robert Y, Skowronski DM. Oculo-respiratory syndrome after influenza vaccination : Trends over four influenza seasons. *Vaccine* 2005;23(28):3726-3732.
- Deinard AS, Ogburn P Jr. (1981). A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. *Am J Obstet Gynecol*; 140:240-5.
- Englund JA, Mbawuike IN, Hammill H, et al. (1993). Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis*; 168:647-56.
- Falsey AR, Treanor JJ, Tornieporth N, et al. (2009). Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis*; 200:172-80.
- Fiore AE et al. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morbidity and mortality weekly report*, 2010, 59(RR 08):1–62.)
- Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, Garcia ML, Krygier A, Costa H, Heining U, Pregaldien JL, Cheng SM, Skinner J, Razmpour A, Saville M, Gruber WC, Forrest B. (2006). CAIV-T Asthma Study Group. 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.
- Fletcher TJ, Tunnicliffe WS, Hammond K, Roberts K, Ayres JG (1997). Simultaneous immunization with influenza vaccine and pneumococcal polysaccharide vaccines in patients with chronic respiratory disease. *British Medical Journal*; 314:1663–5.
- Fowke KR, D'Amico R, Chernoff DN, et al. (1997). Immunologic and virologic evaluation after influenza vaccination of HIV-1-infected patients. *AIDS*; 11:1013-21.
- France EK, Glanz JM, Xu S, et al. (2004). Safety of the trivalent inactivated influenza vaccine among children: a population-based study. *Arch Pediatr Adolesc Med*; 158:1031-6.
- Fuller JD, Craven DE, Steger KA, et al. (1999). Influenza vaccination of human immunodeficiency virus (HIV)-infected adults: impact on plasma levels of HIV type 1 RNA and determinants of antibody response. *Clin Infect Dis*; 28:541-7.
- Gaglani MJ, Piedra PA, Riggs M, Herschler G, Fewlass C, Glezen WP. Safety of the intranasal, trivalent, live attenuated influenza vaccine (LAIV) in children with intermittent wheezing in an open-label field trial. *Pediatr Infect Dis J*. 2008 May;27(5):444-52.
- Glesby MJ, Hoover DR, Farzadegan H, et al. (1996). The effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. *J Infect Dis*; 174:1332-6.
- Gonzalez M, Pirez MC, Ward E, et al. (2000). Safety and immunogenicity of a paediatric presentation of an influenza vaccine. *Arch Dis Child*; 83:488-91.

- Govaert ME, Dinant GJ, Aretz K, Masurel N, Sprenger MJW, Knottnerus JA (1993). Adverse reactions to influenza vaccine in elderly people: randomized double blind placebo controlled trial. *British Medical Journal*; 307:988–90.
- Greene SK, Kulldorff M, Lewis EM, et al. (2010). Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol*; 171:177-88.
- Greene SK, Rett M, Weintraub ES, Li L, Yin R, Amato AA, Ho DT, Sheikh SI, Fireman BH, Daley MF, Belongia EA, Jacobsen SJ, Baxter R, Lieu TA, Kulldorff M, Vellozzi C, Lee GM (2012). Risk of Confirmed Guillain-Barré Syndrome Following Receipt of Monovalent Inactivated Influenza A (H1N1) and Seasonal Influenza Vaccines in the Vaccine Safety Datalink Project, 2009-2010; *Am J Epidemiol*.
- Grilli G, Fuiano L, Biasio LR, et al. (1997). Simultaneous influenza and pneumococcal vaccination in the elderly individuals. *European Journal of Epidemiology*; 13:287-91.
- Groothuis JR, Lehr MV, Levin MJ. (1994) Safety and immunogenicity of a purified haemagglutinin antigen in very young high-risk children. *Vaccine*; 12:139-41.
- Groothuis JR, Levin MJ, Rabalais GP, et al. (1991). Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. *Pediatrics*; 87:823-8.
- Gross PA, Ennis FA, Gaerlan PF, et al. (1977). A controlled double blind comparison of reactogenicity, immunogenicity, and protective efficacy of whole virus and split-product influenza vaccines in children. *Journal of Infectious Diseases*; 136:623–32.
- Gruenberg DA, Shaker MS (2011). An update on influenza vaccination in patients with egg allergy. *Curr Opin Pediatr*. 2011 Oct;23(5):566-72.
- Hak E, Buskens E, van Essen GA, et al. (2005). Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. *Arch Intern Med*; 165:274-80.
- Hambidge SJ, Glanz JM, France EK, et al. (2006). Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA*; 296:1990-7.
- 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.
- Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. (1981). Guillain-Barré syndrome and the 1978–1979 influenza vaccine. *New England Journal of Medicine*; 304:1557–61.
- Institute of Medicine. (2011). *Adverse Effects of Vaccines: Evidence and Causality*. The National Academies Press, Washington D.C., U.S.A; 390-392.
- Izurietta HS, Haber P, Wise RP, Iskander J, Pratt D, Mink C, Chang S, Braun MM, Ball R. (2005). Adverse events reported following live, cold-adapted, intranasal influenza vaccine. *JAMA*; 294(21):2763-5.
- James JM, Zeiger RS, Lester MR, et al. (1985). Safe administration of influenza vaccine to patients with egg allergy. *Journal of Pediatrics*; 106:931–3.
- Juurink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, Manuel DG, Moineddin R, Wilson K. (2006). Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med*; 13;166(20):2217-21
- Kaplan JF, Katona P, Hurwitz ES, Schonberger LB. (1982). Guillain-Barré syndrome in the United States, 1979–1980 and 1980–1981. *JAMA*; 248: 698–700.
- Kelly HA, Skowronski DM, De Serres G, Effler PV. (2011). Adverse events associated with 2010 CSL and other inactivated influenza vaccines. *Med J Aust*; 195 (6): 318-320.
- Kilbourne ED, Arden NH. (1999). Inactivated Influenza Vaccines. In Plotkin SA & Orenstein, WA, eds. *Vaccines*, 3rd ed. Philadelphia, Pennsylvania, WB Saunders Company; 531–552.
- Kramarz P, Destefano F, Gargiullo PM, et al. (2001). Does influenza vaccination prevent asthma exacerbations in children? *J Pediatr*; 138:306-10
- Lasky T, Terracciano GJ, Magder L, et al. (1998). The Guillain-Barré Syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *New England Journal of Medicine*; 339(25); 1797–802.
- Lee-Wong M, Resnick D, Chong KA. (2005). Generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol*. 2005 Jan;94(1):90-4.
- Mader R, Narendran A, Lewtas J, et al. (1993). Systemic vasculitis following influenza vaccination – report of 3 cases and literature review. *Journal of Rheumatology*; 20:1429–31.
- Mak TK, Mangtani P, Leese J, et al. (2008). Influenza vaccination in pregnancy: current evidence and selected national policies. *Lancet Infect Dis*; 8:44-52.
- Margolis KL, Nichol KL, Poland GA, Pluhar RE (1990). Frequency of adverse reactions to influenza vaccine in the elderly: a randomized, placebo-controlled trial. *JAMA: The Journal of the American Medical Association*; 264:1139–41.
- Munoz FM, (2005). Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol*; 192:1098-106.
- Murphy KR, Strunk RC (1985). Safe administration of influenza vaccine in asthmatic children sensitive to egg proteins. *Journal of Pediatrics*, 106:931–933.
- Nakayama T, Onoda K. (2007). Vaccine adverse events reported in post-marketing study of the Kitasato Institute from 1994 to 2004. *Vaccine*;25(3):570-6. Epub 2006 Aug 4
- National Advisory Committee on Immunization (2001). Supplementary Statement on influenza vaccination: Continued use of Fluviral® influenza vaccine in the 2000-2001 season. *CCDR*; 27(ACS-1, 2):1-3.
- Neuzil KM, Dupont WD, Wright PF, et al. (2001). Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. *Pediatr Infect Dis J*; 20:733-40.
- Nichol KL, Margolis KL, Lind A, et al. (1996). Side-effects associated with influenza vaccination in healthy working adults: a randomized, placebo-controlled trial. *Archives of Internal Medicine*; 156:1546–50.
- Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, et al. (1998). Randomized placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet*; 351:326–31.
- Park CL, Frank A (1998). Does influenza vaccination exacerbate asthma? *Drug Safety*; 19:83–8.
- Piedra PA, Yan L, Kotloff K et al. (2002). Safety of the Trivalent, Cold-Adapted Influenza Vaccine in Preschool-Aged Children. *Paediatrics*; 110 (4): 662-672.
- Plotkin S, Koprowski H, Rupprecht CE. (2008). In Plotkin, Orrenstein and Offit (Eds). *Vaccines*: Saunders Elsevier; 687-714
- Pool V, Iskander J. (2006). Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol*; 194:1200; author reply 1201.
- Public Health Agency of Canada. (2005). Oculo-respiratory syndrome following influenza vaccination: review of post-marketing surveillance through four influenza seasons in Canada. *Can Commun Dis Rep*; 31(21):217-25.Reid DW, Bromly CL, Stenton SC, Hendrick DJ, Bourke SJ (1998). A double-blind placebo-controlled study of the effect of influenza vaccination on airway responsiveness in asthma. *Respiratory Medicine*; 92:1010–1.
- Ropper AH. (1992) The Guillain-Barré syndrome. *N Engl J Med*; 326:1130-6

- SAGE (2012). Strategic Advisory Group of Experts. Background Paper on Influenza Vaccines and Immunization. http://www.who.int/immunization/sage/meetings/2012/april/presentations_background_docs/en/index.html
- Sivadon-Tardy V, Orlikowski D, Porcher R, et al. (2009). Guillain-Barré syndrome and influenza virus infection. *Clin Infect Dis*; 48:48-56.
- Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? *Vaccine*. 2009;27(35):4754-70.
- Skowronski DM, Strauss B, De Serres G, MacDonald D, Marion SA, Naus M, Patrick DM, Kendall P. Oculo-respiratory syndrome: a new influenza vaccine-associated adverse event? *Clin Infect Dis* 2003;36:705-13.
- Staprans SI, Hamilton BL, Follansbee SE, et al. (1995). Activation of virus replication after vaccination of HIV-1-infected individuals. *J Exp Med*; 182:1727-37.
- Stowe J, Andrews N, Bryan P, Seabroke S, Miller E. Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study. *Vaccine*. 2011 Nov 28;29(51):9467-72.
- Stowe J, Andrews N, Wise L, Miller E (2009). Investigation of the temporal association between Guillain-Barré syndrome and influenza vaccine and influenza-like illness using the UK General Practice Research Database. *Am J Epidemiol*. 2009 Feb 1;169(3):382-
- Sullivan PS, Hanson DL, Dworkin MS, et al. (2000). Effect of influenza vaccination on disease progression among HIV-infected persons. *AIDS*; 14:2781-5.
- Sumaya CV, Gibbs RS (1979). Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. *J Infect Dis*; 140:141-6.
- Tam JS, Capeding MR, Lum LC, Chotpitayasunondh T, Jiang Z, Huang LM, Lee BW, Qian Y, Samakoses R, Lolekha S, Rajamohanan KP, Narayanan SN, Kirubakaran C, Rappaport R, Razmpour A, Gruber WC, Forrest BD. (2007). Pan-Asian CAIV-T Pediatric Efficacy Trial Network. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed *Pediatr Infect Dis J*; 26(7):619-28
- Tokars JI, Lewis P, Destefano F, Wise M, Viray M, Morgan O, Gargiullo P, Vellozzi C (2012). The Risk of Guillain-Barré Syndrome Associated with Influenza A (H1N1) 2009 Monovalent Vaccine and 2009-2010 Seasonal Influenza Vaccines: Results from Self-Controlled Analyses. *Pharmacoepidemiol Drug Saf*. 2012 May;21(5):546-52. doi: 10.1002/pds.3220. Epub 2012 Mar 8.
- Vellozzi C, Burwen DR, Dobardzic A, et al. (2009). Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. *Vaccine*; 27:2114-20.
- Vesikari T, Karvonen A, Korhonen T, Edelman K, Vainionpää R, Salmi A, Saville MK, Cho I, Razmpour A, Rappaport R, O'Neill R, Georgiu A, Gruber W, Mendelman PM, Forrest B. (2006). CAIV-T Transmission Study Group. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. *Pediatr Infect Dis J*;25(7):590-5
- WER (1999). Recommended composition of influenza virus vaccines for use in the 1991–2000 season. *Weekly Epidemiological Record*; 74:57–61.
- Wise ME, Viray M, Sejvar JJ, Lewis P, Baughman AL, Connor W, Danila R, Giambone GP, Hale C, Hogan BC, Meek JI, Murphree R, Oh JY, Reingold A, Tellman N, Conner SM, Singleton JA, Lu PJ, Destefano F, Fridkin SK, Vellozzi C, Morgan OW (2012). Guillain-Barré Syndrome During the 2009-2010 H1N1 Influenza Vaccination Campaign: Population-based Surveillance Among 45 Million Americans. *Am J Epidemiol*. 2012 May 11. [Epub ahead of print]
- 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-S741.
- Zaman K, Roy E, Arifeen SE, et al. (2008). Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*;359:1555-64.