HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 3, 657–670
https://doi.org/10.1080/21645515.2017.1423153

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REVIEW

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# Influenza vaccines: Evaluation of the safety profile

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**ABSTRACT**

The safety of vaccines is a critical factor in maintaining public trust in national vaccination programs. Vaccines are recommended for children, adults and elderly subjects and have to meet higher safety standards, since they are administered to healthy subjects, mainly healthy children. Although vaccines are strictly monitored before authorization, the possibility of adverse events and/or rare adverse events cannot be totally eliminated.

Two main types of influenza vaccines are currently available: parenteral inactivated influenza vaccines and intranasal live attenuated vaccines. Both display a good safety profile in adults and children. However, they can cause adverse events and/or rare adverse events, some of which are more prevalent in children, while others with a higher prevalence in adults.

The aim of this review is to provide an overview of influenza vaccine safety according to target groups, vaccine types and production methods.

**ARTICLE HISTORY**
Received 2 October 2017
Revised 30 November 2017
Accepted 23 December 2017

**KEYWORDS**
adverse events; influenza vaccines; safety; vaccine types; age-groups

## Introduction

Vaccination is the most effective method of controlling seasonal influenza infections and the most important strategy for preventing possible pandemic events.[1] Influenza vaccines are recommended for children, adults and elderly subjects.[2] Since vaccines are mainly administered to healthy people, they need to comply with a higher safety standard. In addition, as they are used to immunize a considerable part of the population, rare adverse events (AEs) may affect a significant number of individuals.[3,4]

A "vaccine AE" or an "AE following immunization" is defined as "*any untoward medical occurrence which occurs during administration of a vaccine or follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom or a disease*".[5] AEs also include those events associated with vaccination errors and reactions correlated with anxiety and product quality defect.

The terms "adverse drug reaction" and "adverse vaccine reaction or effect" are both used to indicate that the development of the AE has a causal relationship with the medicinal product, as indicated by consistent scientific evidence.[6] The identification of potential serious adverse reactions during clinical trials can evoke significant changes in the manufacturing process, especially if these reactions are fatal or life-threatening; in such cases, regulators should be promptly informed. It is recommended that the old term "side effects", which was used to indicate both favorable (positive) and unfavorable (negative) effects, should no longer be used, or at least not as a synonym for the terms "adverse event" or "adverse reaction".[7] Moreover, the terms "severe" and "serious" do not have the same meaning. Indeed, whereas the former is usually used to indicate the severity of a particular event, which may have minimal medical importance, the latter identifies the outcome of the patient or the measures required to deal with the reactions that threaten the patient's life or functions; these serious reactions are subject to obligatory reporting.[7]

Before a vaccine is licensed, its safety is evaluated in different phases of clinical trials; it subsequently undergoes post-licensure surveillance.[8]

Vaccine safety may differ according to the target group, the genetic predisposition of the population and the type of vaccine.[9]

Although vaccines are strictly monitored before authorization, the possibility of AEs due to annual changes in vaccine formulations, vaccine administration patterns, environmental factors or genetic factors of the host cannot be totally eliminated. Consequently, annual post-licensure vaccine safety surveillance is fundamental.[10] With regard to extremely rare events (1 case every 10,000 vaccinations),[11] the relatively low number of cases available for analysis constitutes a study limitation. If no event of concern is registered in a study (i.e. a zero numerator is reported), it is necessary to conduct further investigations. Indeed, a zero numerator does not mean the absence of risk.[12] In the case of a vaccine, AEs can only be reliably identified after larger populations have been vaccinated. For this reason, post-marketing surveillance is fundamental. Recently, an increased incidence of narcolepsy was reported in six European countries following vaccination with Pandemrix against pandemic influenza A virus, A(H1N1)pdm09 ("swine flu"),

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during the winter 2009–2010 (see below). The recent systematic review and meta-analysis conducted by Sarkanen and coll.[13] in order to investigate the incidence of narcolepsy related to H1N1 vaccination revealed that Pandemrix was the only vaccine associated with an increased risk. The relative risk of narcolepsy was 5- to 14-fold higher in children/adolescents and 2- to 7-fold higher in adults in the first year following immunization. Furthermore, investigations conducted in Finland and Sweden seemed to demonstrate that the risk of narcolepsy extended into the second year after vaccination, although further data are necessary to confirm this hypothesis. In addition to post-marketing surveillance, enhanced safety surveillance (ESS) is required by the European Medicines Agency (EMA) for all seasonal influenza vaccines, in order to improve the rapid detection of clinically significant changes in the safety profile of flu vaccines.[14,15] It is recommended that ESS is included in routine pharmacovigilance activities if the vaccine is used for the first time and is administered to all age-groups (e.g. subjects aged 6 months to 5 years, 6 to 12 years, 13 to 18 years, ≥ 18 years-65 years and > 65 years).[14]

In Europe, vaccine safety is monitored by the Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium, and in the United States by the Centers for Disease Control and Prevention (CDC) through the routine use of two surveillance systems: the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).[16]

In addition to national surveillance organizations, the World Health Organization (WHO) has established a global system for international drug monitoring – the Uppsala Monitoring Center (UMC) and the Global Advisory Committee on Vaccine Safety (GACVS) – in order to address vaccine safety issues of potential global importance in a scientifically accurate manner.[3,4,17] The surveillance of influenza vaccine safety in terms of post-marketing adverse drug events is usually prompted by spontaneous reporting. While North America and Europe have the most advanced information systems for the assessment of drug safety upon licensing and population coverage, Asian countries are making good progress.[18]

The aim of this review is to provide an overview of vaccine safety according to target groups, vaccine types and production methods.[9]

## Vaccine types and production methods

The safety of vaccines is a critical factor in maintaining public trust in national vaccination programs. This is especially true of influenza vaccines, the composition of which needs to be evaluated twice a year in order to ensure antigenic matching between the viral strain contained in the vaccine and the circulating strain.[19] Two main types of influenza vaccines are currently available and are administered by different routes: parenteral inactivated influenza vaccines (IIVs) and intranasal live attenuated influenza vaccines (LAIVs). The former have been used for more than 50 years, are licensed for use in subjects aged ≥6 months and display a good safety profile; the latter are licensed in Europe for children from 2–17 years of age and induce a broader immune response involving both local and systemic antibody and T-cell responses.[20]

### Inactivated Influenza Vaccines

IIVs have been manufactured and used since 1940, and are the most common influenza vaccines. Until 2015, vaccine producers were required by EMA committee to perform annual clinical trials in order to evaluate both immunogenicity and safety for the updating of seasonal annual IIVs.[21] Clinical trials are no longer required for lineage changes of licensed IIVs.[22] Inactivated vaccines have an excellent safety profile, and are recommended for children of ≥6 months of age, the elderly, asthmatics and those individuals with other high-risk conditions.

### Trivalent Influenza Vaccines

Trivalent influenza vaccines (TIVs) (containing A/H1N1, A/H3N2 and one B lineage) have been manufactured since 1978, replacing the bivalent inactivated influenza vaccines that had been widely used since 1944 (Table 1).[23]

During the 1990–2006 and 2008–2009 influenza seasons, Muhammad et al.[24] investigated possible new or unexpected AEs following TIV administration to children aged 2 to 17 years and 5 to 17 years, respectively. From 1990 to 2006, 2,054 cases of vaccine AEs were reported, peaking in the 2003–2004 influenza season, whereas 506 were reported in 2008–2009. Higher proportions of medication errors and Guillain-Barré Syndrome (GBS) were observed, although the latter could not be causally correlated with vaccination. Among 201 reports regarding medication errors, 94% did not cause AEs other than the medication error itself.

TIV vaccination is recommended for children older than 6 months and between 6 and 59 months with a predisposition to severe influenza in Australia and Western Australia, respectively.[25] In 2010 in Australia, an increase in febrile convulsions (FCs) was observed after TIV immunization; however, this involved only one brand, produced by bioCSL (Fluvax and Fluvax Junior). Subsequently, Li-Kim-Moy and coll.[26] reviewed the safety of TIV administration. Specifically, they investigated the rates of fever, FCs and serious AEs reported in both unpublished and published clinical trials conducted on children during the period 2005–2012. The incidence of fever or AEs caused by TIV was low, whereas higher fever rates were correlated with bioCSL influenza vaccines in young children. However, it was not possible to attribute this to the TIV strain composition. This study highlights the necessity to strictly monitor seasonal influenza vaccine safety and to report post-administration data accurately.[26] A recent study conducted by Esposito et al.[27] investigated the tolerability and safety of TIV in overweight and obese children between 3 and 14 years old, since obesity is an important risk factor for infections that are facilitated by respiratory diseases. In overweight/obese children, the antibody response upon TIV vaccination was similar to or slightly greater than that observed in normal-weight subjects of similar age, and this situation persisted for at least 4 months after vaccine administration. The incidence of local and systemic reactions was comparable between the groups,

**Table 1.** Vaccine types and route of administration.

| Vaccine types | Route of administration |
|---|---|
| TIV | Parenteral Intradermal |
| QIV | Parenteral |
| LAIV | Intranasally |

and no serious AE was observed, confirming that influenza vaccines have a good safety profile even in overweight/obese children.[27]

### Quadrivalent Influenza Vaccines

In addition to the 3 strains present in TIV, namely H1N1 and H3N2 influenza A subtypes and influenza B, the formulation of Quadrivalent Influenza Vaccines (QIVs) contains two additional influenza B lineages, Yamagata and Victoria, which have been spreading since 1985 and have reduced the efficacy of TIV.[28] QIVs should enhance protection against influenza B by avoiding the possibility of a B strain mismatch. The first quadrivalent LAIV was licensed in 2012 and, after several QIV formulations had been tested, it entered the market (Table 1).[29]

The WHO recommended both B lineages for inclusion in the 2012–2013 influenza seasonal vaccine in the Northern hemisphere. In the US, 4 QIVs have recently been approved: the three inactivated vaccines *Fluarix*$^{TM}$, *FluLaval*$^{TM}$ (both GlaxoSmithKline Vaccines) and *Fluzone*® (Sanofi Pasteur) and the LAIV *FluMist*® (MedImmune).[30] In a phase-II multi-center study conducted on healthy adults aged ≥18 years, Greenberg et al.[31] compared the safety and immunogenicity of a QIV whose formulation contained two influenza B strains versus licensed TIVs containing either a Victoria B-lineage strain (2009-2010 TIV) or a Yamagata B-lineage strain (2008-2009 TIV). Seroprotection, seroconversion and AEs were comparable in all groups.

Pépin and coll.[32] investigated the immunogenicity and safety of a prototype inactivated QIV immunization (containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage) and B/Florida/04/2006 (Yamagata lineage) strains) in comparison with both a licensed 2011–2012 TIV (containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008 (Victoria lineage) strains) and an investigational TIV (containing the alternative B strain lineage B/Florida/04/2006 (Yamagata lineage), the A/California/07/2009 (H1N1) and A/Victoria/210/2009 (H3N2) strains). They conducted a phase-III, randomized, active-controlled, multi-center trial involving 1568 adults during the 2011/2012 influenza season. All groups had similar pre-vaccination HAI antibody titers and showed an increase following immunization. Antibody responses following QIV administration were not inferior to those elicited by the TIVs for all the matched strains. Moreover, the QIV was able to induce higher antibody responses against the B strains not contained in the TIVs. All the strains contained in the QIV met the EMA criteria for both age-groups of subjects (18-60 years and > 60 years). With regard to the TIVs, however, only the A and matched B strains met all EMA criteria; the unmatched B strains did not. The fact that all three vaccines evoked higher responses and response rates in the younger adults than in the elderly adults is in agreement with the literature, and is due to the waning responsiveness of the elderly immune system and to other aging- factors.[33,34] A meta-regression study conducted by Beyer and coll.[35] further confirmed that the benefit of QIV depends on age. Indeed, they observed that the impact of B lineage mismatch was negatively associated with pre-seasonal immunity. Infants and children benefited most from QIV since they had not yet been exposed to influenza B; accordingly, vaccine effectiveness declined as pre-seasonal immunity increased. QIV administration may therefore provide less significant protection in the elderly than in the young in the case of lineage mismatch.

The safety and reactogenicity of QIV have proved similar to those of seasonal influenza vaccines, as demonstrated by Tinoco et al.[36] The most common adverse reactions were pain at the injection site, headache and myalgia, all of which disappeared within 3 days of vaccination. No serious AE or death were registered.

Similar results regarding the safety of the first QIV introduced in Australia were reported by Regan et al.[37] in a sample of 1,685 healthcare providers (HCPs). Although 7 days after immunization no AE was observed in either QIV- or TIV-vaccinated subjects, a slightly but significantly higher percentage of QIV-immunized than TIV-immunized HCPs reported pain or swelling at the injection site. That study confirmed the safety of QIV, since its reactogenicity was similar to that of TIV. The meta-analysis recently conducted by Moa and coll.[38] also showed no significant differences between the safety profiles of QIV and TIV, except for a slightly higher rate of injection-site pain following QIV immunization, which may have been due to the higher dose (60 versus 45 mcg), in agreement with the results of the study by Regan.[37]

It has been suggested that differences in production methods yielding vaccines of different composition – in addition to the presence of a further antigen in QIV – may be responsible for the different frequency of AEs.[37] However, although QIV elicited slightly more local reactions (injection-site pain) than TIV, the potential benefit of QIV in protecting the population from infection is considered to be greater.[38]

The safety and reactogenicity profile of inactivated QIV in children aged 18–47 months was evaluated by Rodriguez Weber and coll.[39] in a phase-II double-blind study. Reactogenicity was investigated since QIV contains 60 $\mu$g of antigen compared with 45 $\mu$g in TIV. Serious AEs were monitored for 6 months after immunization. The reactogenicity and safety profiles of QIV were similar to those observed for TIV.

An investigation on the VAERS reports following vaccination with IIV4 and trivalent IIV3 from 7/1/2013 to 5/31/2015 was conducted by Haber et al.,[40] who reported similar safety profiles between the two vaccines. This observation was in agreement with the data obtained from pre-licensure studies of IIV4. Most of the AEs reported were non-serious. Among the most frequent AEs in persons aged between 6 months and 17 years, were fever, injection-site swelling and erythema, whereas pain in the extremities and injection-site pain were most frequent in individuals aged 18–64 years. The most common non-lethal serious events were GBS, seizures, injection-site reactions and anaphylaxis.

### Live attenuated influenza vaccines

LAIVs have been used in Russia for decades, and were licensed in the US in 2003 for healthy subjects aged 2–49 years[41] and in Europe in 2012 for healthy children aged 2–17 years. They are able to induce a stronger immune response than IIV by mimicking natural infection (see below).[20] Since they are administered intranasally, several adaptive immune responses, such as serum antibodies, mucosal and cell-mediated immunity are

induced.[42] The evoked immune response directed towards neuraminidase and hemagglutinin glycoproteins is similar to that elicited by the process of naturally occurring infection.[43,44] The fact that a higher incidence of infections involving the lower airways was not observed supports the notion that the virus is unable to replicate and induce pathology in the respiratory tract.[45,46] Consequently, protection against the virus contained in the vaccine formulation and mismatched strains is induced by LAIVs.[47] The development of severe influenza following LAIV immunization is prevented, since the vaccine contains a cold-adapted influenza virus that is unable to replicate in temperature conditions >37.8°C.[43,44] LAIV is not recommended in elderly or immunosuppressed subjects or in those who are caring for persons in whom severe influenza disease carries high risk. LAIVs are not recommended for children < 2 years of age, as, in early investigations, the administration of LAIVs to this age-group promoted the onset of wheezing. Furthermore, LAIVs are contraindicated in severe asthmatics currently on oral or high-dose inhaled glucocorticosteriods or who have active wheezing.[47,48]

Concomitant immunization with other usual childhood vaccines has been shown not to influence the immune response induced by LAIV in healthy young children.[49]

Furthermore, LAIVs proved to be more effective than TIV in reducing the incidence of influenza illness in two open-label studies conducted on children aged 6–71 months affected by recurrent respiratory tract illnesses and in children and adolescents with asthma aged 6–17 years.[49] LAIV displays a good safety profile, comparable to that of TIV.[46,50-53]

LAIV vaccinees show the presence of the vaccine virus, but the risk of transmitting the virus to household members is marginal, ranging from 0.58% to 2.87%. In only one case has the transmission of LAIV virus to a placebo recipient been reported. In that case, however, transmission did not induce the disease.[54] It has been observed that, in children aged 9–36 months, the presence of the virus is highest 3–5 days after vaccination, reaching up to 80%, whereas it is lower in adults affected by HIV (1.8%).[55] Furthermore, not only do LAIVs elicit direct protection in vaccinated subjects, they also promote indirect protection by reducing the transmission of the influenza virusamong subjects belonging to clinical risk groups.[56] LAIVs have been reported to cause adverse effects in 15% of cases. However, these are not serious: nasal congestion, runny nose and slight fever in adolescents, and sore throat in adults. With the exception of fever, which has been reported on the day after vaccination, the other symptoms occur 2–3 or 8–9 days after LAIV administration.[45] LAIVs have been reported to cause slightly more troublesome moderate adverse effects than TIV, though the incidence of these is low. The difference was significantly higher following the first dose, but disappeared after the second administration[48] and was reduced following the subsequent annual vaccinations. Although one of the most frequent side effects in young children was wheezing, no difference in severity, length of hospitalization or treatment was observed.[45,48] Furthermore, asthma episodes occurring in LAIV vaccinees showed a 4-fold increase in comparison with controls in the 42 days after vaccination.[45]

Severe consequences have rarely been reported, and have displayed a similar frequency after LAIV, TIV and placebo; no association with vaccine administration has been proved. Recently, McNaughton's group investigated the incidence of adverse effects of interest (AEIs) in children and adolescents upon immunization with nasal QLAIV (Fluenz Tetra, Astra Zeneca) in the same influenza season in England. They reported nasal congestion, cough and malaise among the most frequent AEIs. No serious AE, hospitalization or death was reported during the investigation.[57]

Since a higher frequency of fever has been reported after LAIV than after IIV vaccine administration, a recent prospective observational study conducted by Stockwell's group[58] investigated the frequency of fever following immunization of young children with IIV in 3 community clinics in New York City. A low frequency of fever was found and no difference between the vaccines evaluated was observed during the 2013–2014 influenza season.[58]

The studies conducted by Carr et al.[59] and King et al.[60] confirmed the safety of LAIV in children affected by cancer and in HIV-infected adults, respectively.

However, discordant data on the efficacy of LAIV have emerged between the US and Europe.[61] Specifically, owing to ineffectiveness during the previous three seasons (2013–2014, 2014–2015 and 2015–2016),[62] the use of LAIV was not recommended in the US during the 2016–2017 influenza season, and the recommendation not to use LAIV has been renewed for the 2017–2018 flu season.[63] Conversely, many other health authorities, including those in the UK and Canada, consider the efficacy of LAIVs to be adequate. Several factors have been hypothesized to have played a role in the diminished vaccine effectiveness, including methodological issues in the studies.[64]

### LAIV in egg-allergic individuals, asthmatic subjects or children with recurrent wheezing

Until recently, few safety data regarding LAIV administration in egg-allergic young children were available, although egg allergy is relatively common, affecting between 2–6% of preschool children.[65]

In the US, the prevalence of asthma[66,67] and egg allergy[68] has prompted vaccine manufacturers to tackle the problem of immunizing egg-allergic patients in whom vaccination with egg-containing influenza vaccine is recommended.

In the 1970s, egg-allergic patients had to undergo skin testing with the influenza vaccine[69-71]; if the result was negative, they could be safely immunized, otherwise vaccination was not recommended. However, a subsequent study conducted by Murphy and Strunk[72] found that influenza vaccination was safe even in the event of a positive skin-test result if a protocol of multiple, graded injections was implemented, whereas Zeiger[73] suggested that influenza vaccine skin tests (prick and intradermal) should be carried out before vaccine administration in individuals with a history of adverse reactions to eggs and positive skin-test results. A single dose could be administered if the influenza vaccine skin-test results were negative, while a 2-dose graded or desensitization protocol should be implemented if they were positive.[73,74] The safety of administering the influenza vaccine in a graded 2-dose fashion to egg-allergic children without performing the vaccine skin test was investigated by

Chung and coll.[75] in a retrospective chart-review study, which suggested that the skin test could safely be omitted.

A recent investigation conducted by Turner et al.[65] found a low risk of systemic allergic reactions following LAIV immunization in subjects aged 2–18 years during the influenza season 2014–2015 in the UK; 35% of the children had a history of anaphylaxis to eggs. Immediate AEs following LAIV immunization were mild and self-limiting; these were: contact/localized urticaria, rhinitis and oropharyngeal itching. Delayed adverse effects potentially correlated with LAIV were lower respiratory tract symptoms, which occurred within 72 hours of vaccination. This higher incidence was reported in young children, but it did not reach statistical significance. Delayed events were not associated to any risk factor. In addition, the vaccine was well tolerated by asthmatic subjects and those under 5 years of age who were affected by recurrent wheezing[65]; this finding is in agreement with those of other studies.[46,48,50,76-78] However, certain guidelines in North America do not currently recommend its use in subjects of this age who have had an episode of wheezing in the previous year.[79]

### *Pandemic influenza vaccines*

Any pandemic influenza vaccine may have an incompletely described safety profile.[80] A correlation between influenza vaccines and GBS has been reported by several studies – in 1976[81] and in 1992–1994[81-83] – and by three meta-analyses.[84-86] The authors of these last studies reported a 2–3-fold higher risk of GBS in subjects vaccinated with either adjuvanted or non-adjuvanted A(H1N1)pdm09 vaccines in comparison with unvaccinated subjects. However, contrasting results have also been reported.[87-90] The potential adverse effect of A(H1N1)pdm09 monovalent or trivalent vaccination was also assessed by Alcalde-Cabero and coll.,[91] but no association was found.

Recent epidemiological investigations have confirmed the association between an AS03-adjuvanted pandemic influenza vaccine (Pandemrix, GlaxoSmithKline Biologicals, Germany) and the onset of narcolepsy in children and adolescents.[92] The novel circulating A(H1N1) influenza virus was identified in April 2009 and quickly spread worldwide in June 2009. Millions of A(H1N1) pandemic vaccine doses were produced within a narrow time-window (from April 2009 until November of the same year). One year after the European AS03-adjuvanted A(H1N1) pandemic vaccine was authorized in Europe, a higher number of narcolepsy cases was observed in Sweden and Finland (9.0/100,000 incidence in vaccinees versus 0.7 in unvaccinated subjects),[92-95] and also in other countries.[11,96] It was hypothesized that a peptide located on a surface-exposed region of influenza nucleoprotein A was characterized by protein residues similar to the first extracellular domain of hypocretin (HCRT) receptor 2. In accordance with this hypothesis, a higher frequency of antibodies to HCRT receptor 2 was found in sera from narcoleptic Finnish patients immunized with the European AS03-adjuvanted vaccine Pandemrix[92] than in unvaccinated subjects. Furthermore, a cross-reaction between HCRT receptor 2 and influenza nucleoprotein was described. No persistent antibody response to nucleoprotein was detected in sera from non-narcoleptic subjects vaccinated with Focetria (a vaccine differently produced), which contained 72.7% less influenza nucleoprotein. Thus, differences in vaccine nucleoprotein content and the respective immune response could explain the correlation between narcolepsy and Pandemrix.[97]

A recent study[98] investigated the annual frequency of anaphylaxis following immunization, a rare AE which can be life-threatening and causes hospitalization within 48 hours after immunization. The study was conducted on subjects younger than 18 years in Germany between June 2008 and May 2010. Of the 22 cases of anaphylaxis evaluated, 8 were due to the administration of AS03-adjuvanted A/H1N1 pandemic influenza vaccine. This vaccine was associated with a higher risk of anaphylaxis than other vaccines, with an incidence of 11.8 of cases per 1,000,000 doses administered.

## Age-groups

While influenza viruses infect all age-groups, children and adults over the age of 65 years are most at risk. Vaccination is recommended for these age-groups, for pregnant women, for subjects with high-risk conditions due to complications of influenza and for those with chronic medical conditions (metabolic, cardiac, pulmonary or kidney diseases, and immunocompromised patients). The same recommendation is generally extended to nurses and healthcare workers.[99,100]

Most influenza vaccines are safe in adults and children. However, they can sometimes cause AEs. According to the age-group, AEs may include fever, vomiting, nausea, headache, irritability, injection site reaction and rash.[9,100]

## Children

Infants and children (particularly those younger than 5 years old) are especially susceptible to influenza infection and its complications, such as pneumonia. These subjects play a primary role in the transmission of influenza viruses, since they acquire and release greater amounts of virus than adults.[101-103]

In 2003 in the US, influenza vaccination was officially recommended for healthy children aged 6–23 months, and in 2008 “universal” vaccination of all subjects over 6 months of age was recommended.[102,104]

The scenario is different in Europe, where, despite several recommendations by international experts and advisory groups, pediatric vaccination has not reached a satisfactory level.[105]

Worldwide, TIVs are currently the only injectable preparations authorized for pediatric use in children above 6 months of age.[101]

Several studies have evaluated the safety of TIVs in healthy children, and have found a good safety profile with no serious AEs.[106-109] The most common solicited local reactions are pain and redness at the injection site, while the most common solicited systemic reaction is irritability, followed by malaise and headache (Table 2).[107-110]

In the USA, the recommended dose for children below 3 years of age is half of the adult dose. However, several studies have provided evidence that the administration of a full dose is safe in children and does not increase reactogenicity.[107,108,110] More specifically, local reactions are more common in toddlers than in infants, and in full-dose vaccinees, though the differences are not significant.[108] As stated above, the most commonly

**Table 2.** Most common local and systemic reactions in children.

| Children | | |
|---|---|---|
| Vaccine | Local reaction | Systemic Reaction |
| TIV | Pain<br>Redness<br>Tenderness | Irritability<br>Malaise<br>Headache |
| adjuvanted TIV | Pain<br>Tenderness<br>Erythema<br>Induration | Irritability<br>Diarrhea<br>Crying<br>Fatigue<br>Chills<br>Headache<br>Fever<br>Myalgia |
| LAIV | Nasal congestion | Fever<br>Decreased activity |
| Pandemic | Pain<br>Redness<br>Swelling | Malaise<br>Fatigue<br>Myalgia |

reported systemic reaction is irritability, whereas the most common local reactions are redness and tenderness in the first 3 days after vaccination.[107,108] Concerning other local reactions, swelling and induration more frequently occur after a full dose, but are less commonly reported.[108]

In addition, cell-derived influenza vaccines are also well-tolerated and have a good safety profile – comparable to that of egg-derived influenza vaccines – in children.[111,112] Pain at the injection site is the most common local reaction, while the most commonly reported systemic reactions are: malaise in the 4-8-year-old cohort and headache among 9-17-year-olds (Table 1).[112]

Esposito et al.[113] evaluated the safety and reactogenicity of intradermal (ID) influenza vaccine, an alternative route of injection to the traditional intramuscular (IM) modality, in children older than 3 years. Although local reactions were more common in the cohort of ID vaccinees than in the IM vaccine group, they were transitory and did not become more frequent as the vaccine dose increased.

However, the efficacy of TIVs is not completely satisfactory in children. For this reason, adjuvanted vaccines have been developed in order to improve the immune response. Clinical studies have demonstrated the great advantage of these vaccines, which are able to induce an enhanced immune response in children, even against B strains, in the case of low pre-immunization titers and mismatching viruses.[1] Overall, adjuvanted vaccines induce slightly higher local and systemic reactogenicity than TIVs; however, the reactions are mild and transient, and there is no increase in unsolicited AEs.[114-118] In children younger than 36 months, the most commonly reported local reactions are injection-site pain, tenderness and erythema (Table 2),[114,115,117] while the most common systemic reactions are irritability, diarrhea and crying (Table 2).[114,117] In older children injection-site pain, erythema and induration are the most common local reactions, while systemic reactions are: fatigue, chills, headache, fever and myalgia (Table 2).[114,116,117] Fever displays a higher incidence after the second dose.[116] Overall, children older than 36 months display a higher incidence of solicited reactions than younger children.[114]

Recently, seasonal inactivated QIV containing both the Victoria and Yamagata lineages of the B virus have been marketed; these have shown a superior antibody response against the additional B strain and immunogenicity comparable to the traditional TIVs.[1,119] In children aged 6–35 months, their safety profile is acceptable and similar to that of TIVs, and their reactogenicity seems not to be excessive on increasing the amount of influenza antigen.[120,121]

The other licensed vaccine is the LAIV, which is administered intranasally to persons aged 2–49 years in the USA, Europe, India and Russia. The advantages of the LAIV vaccine are its ability to mimic the natural pathway of infection, to induce a broader humoral and cellular response than TIV and to provide protection against both well-matched and antigenically drifted strains.[1] The most frequently reported reaction is nasal congestion[57,122] together with low-grade fever and decreased activity (Table 2).[122] These symptoms did not occur after the second dose.[122] While no serious AE has been reported,[122-124] McNaughton et al.[57] reported asthma in a large number of study participants, which suggests that quadrivalent LAIV should not be administered to children or adolescents with severe asthma or active wheezing.

Vaccination remains the most effective strategy for preparing for seasonal infections and for a possible pandemic. The WHO guidelines state that, whenever possible, the safety of pandemic vaccines should be evaluated before the pandemic. However, the safety profile of a pandemic influenza vaccine may not be completely investigated.[80,125]

Most of the pandemic vaccines against the H1N1 pdm09 influenza virus have been evaluated. Overall, they have shown a clinically acceptable safety profile, without any serious AEs or potentially immune-mediated diseases.[126-128] As for the other vaccines, the most commonly reported local reaction is injection-site pain, together with redness and swelling (Table 2).[127-131] The most frequent systemic reactions are malaise, fatigue and myalgia (Table 2).[127,132] Plennevaux et al.[131] reported that headache, myalgia and malaise were more common in children older than 24 months, while irritability, abnormal crying, loss of appetite and drowsiness occurred more frequently in children younger than 24 months. The most common unsolicited AEs are upper respiratory tract infection[126,127] and nasopharyngitis.[127] Adjuvanted and non-adjuvanted H5N1 vaccines are safe and well tolerated, though Diez-Domingo et al.[133] reported one potential immune-mediated disease (autoimmune hepatitis) related to vaccination.

## Adults and the elderly

Influenza vaccination is generally recommended for the elderly, as they are at risk of, and more vulnerable to, influenza complications.[134] The European guidelines do not include other groups among those recommended for vaccination, though vaccination has been strongly suggested for caregivers and healthcare workers.[135] However, influenza disease in adults carries a significant societal cost in terms of absence from work and lost productivity.[136,137]

Several studies have evaluated the safety profile of egg/cell-derived, adjuvanted/non-adjuvanted influenza TIV and QIV in adults and elderly subjects. Overall, the vaccines showed a

robust safety profile and acceptable reactogenicity. Injection-site pain is the most frequently reported local symptom (Table 3).[31,136,138-143] The most frequent systemic reactions in both adults and the elderly are fatigue, headache and myalgia (Table 3).[31,136,140-146] Only one study reported fever as the most common solicited reaction.[139] Rates of solicited local and systemic reactions are higher in adults than in the elderly[31,139,141,142,145,147,148] and in females than in males.[145] Unsolicited AEs are nasopharyngitis and cough.[31,136,138,146] Overall, no serious AEs or deaths related to influenza vaccination are reported[31,142,143,145,146,149] with the exception of two studies. The first of these[136] described serious AEs in the QIV group (myocardial infarction and cerebrovascular accident) and the TIV group (pneumonia, cerebrovascular accident, nephrolithiasis and arteriosclerosis). The second[138] reported one death, possibly related to vaccination, and SAEs (bronchitis, asthmatic crisis, chronic obstructive pulmonary disease and GBS) possibly or probably related to vaccination with TIV, with and without adjuvant.

The ID vaccines are well tolerated in adults and the elderly and have not raised safety concerns.[137,150] Malaise and headache are reported to be the most frequent systemic reactions[137,151] and their profile is similar to that of vaccines injected via the IM route.[152,153] Local reactogenicity is reported to be higher after ID vaccination than after IM vaccination[137,152,153] even when subjects are re-vaccinated with ID vaccine.[137] Swelling appears to be more common in the case of ID vaccination in the previous year.[137]

LAIV, whether trivalent or quadrivalent, is safe, without any increased risk after administration.[124,154] The vaccine is currently approved in the USA, Europe, India and Russia for subjects aged 2–49 years. However, it has also been evaluated in adults and the elderly.[155,156] Reactions after LAIV vaccination include cough, sore throat, runny rose/nasal congestion and decreased appetite.[155,156] No significant AEs following LAIV vaccination have been reported[51] with the exception of upper and lower respiratory tract infections, wheezing, rhinitis and sneezing.[124,156,157]

With regard to children, most of the pandemic vaccines, with or without adjuvant, are against the pandemic H1N1 influenza virus.[158-164] However, pre-pandemic vaccines, such as those against H5N1, H7N9 and H5N1, including LAIV, have also been evaluated.[165-167] Overall, these vaccines have displayed good tolerability and satisfactory safety profiles.[158,160,162-164] The most common local reaction is injection-site pain, while systemic events are fever, headache, malaise, myalgia and fatigue.[111,158-161,163,164] After the second dose, both types of reaction are similar to those seen after the first, or are attenuated.[111,161,164]

**Table 3.** Most common local and systemic reactions in adults and the elderly.

| Adult - Elderly | | |
|---|---|---|
| Vaccine | Local reaction | Systemic Reaction |
| TIV/QIV | Pain | Fatigue |
| adjuvanted-non adjuvanted | | Myalgia<br>Headache |
| LAIV | Cough<br>Sore throat<br>Runny rose/nasal congestion | Decreased appetite |
| Pandemic | Pain | Fever<br>Headache<br>Malaise<br>Fatigue<br>Myalgia |

## High-risk individuals

Individuals of any age with certain medical conditions are at increased risk of influenza-related complications than the general population. Vaccination remains the most effective method of controlling and preventing influenza infections, and health authorities have included individuals with chronic medical conditions among those recommended for influenza vaccination.[168] The only authorized vaccine for this target group is TIV, as the safety of LAIV has not been established.[169] However, despite the recommendation, vaccination coverage remains low among high-risk individuals.[170]

Several studies have evaluated the safety profile of seasonal and pandemic influenza vaccines in high-risk individuals and have shown that vaccines are well tolerated and safe in this target group.[27,152,171-176] However, the conventional vaccines are reported to induce a poor immune response in high-risk individuals, and different strategies, such as administration of a high-dose booster, the use of adjuvants and ID administration, have been evaluated.[173]

Standard doses, high doses and booster doses of TIV have proved safe and well tolerated in high-risk adults, such as hematopoietic stem cell transplantation patients, individuals with type 2 diabetes, solid transplant recipients, patients with multiple myeloma and with Duchenne muscular dystrophy; no unexpected serious AEs have been recorded.[171-173,177,178] Specifically, the most common local reaction is pain at the injection site, while the most frequently reported systemic reactions are myalgia and general malaise (Table 4). No significant differences in local and systemic reactions between high-risk individuals and control groups have been reported.[171,177] Two studies, however, detected a trend towards a lower incidence of local and systemic reactions in patients with type 2 diabetes after seasonal vaccination and in those with Duchenne muscular dystrophy after pandemic vaccination.[173,179] There are no safety concerns regarding the administration of ID vaccines in high-risk individuals, such as HIV-infected adults and immunocompromised patients. However, local and systemic reactions are higher with ID than IM formulations.[152,172]

The safety of seasonal and pandemic influenza vaccines in children with underlying medical conditions has been proven,

**Table 4.** Most common local and systemic reactions in high-risk individuals.

| High-risk individuals | | |
|---|---|---|
| Vaccine | Local reaction | Systemic Reaction |
| TIV | Pain | Myalaise<br>Myalgia |
| Pandemic | Pain<br>Tenderness | Fatigue<br>Decreased activity |

and no severe AEs have been reported.[27,113,174-176,180,181] The most common local reactions are pain[174,180] and tenderness, while systemic reactions consisting of fatigue and decreased general activity have been noted (Table 4).[180] Studies have revealed that standard-dose TIV in overweight and obese children and high-dose TIV in children and young adults with cancer induce more solicited reactogenicity events, though the difference is not statistically significant.[27,175]

## Conclusions

Influenza is still a substantial cause of death and suffering during the winter months, and imposed a heavy socioeconomic burden, especially in young subjects and the elderly.[134] Although vaccination remains the single best defense against influenza and its complications, in many European countries, vaccination coverage is suboptimal, especially in comparison with the US. This has serious consequences, such as the evident excess mortality registered in Italy in elderly subjects who were not vaccinated against influenza in 2015[182] These data, which should be confirmed by further investigations, highlight the necessity to increase rates of immunization through the planning and implementation of public health interventions. Furthermore, a higher standardization of vaccine strategies has been observed in the US than in European countries[183] Although influenza vaccines display a good safety profile, a growing number of people shun vaccination for fear of negative side effects,[92] such as the onset of autoimmune conditions. This fear, in addition to the public's misperceptions concerning adjuvants and their role, have discouraged vaccination not only against influenza but also against other infectious diseases, allowing them to re-emerge.[92] A significant element in the overall effectiveness of vaccines is therefore their acceptance by the public.[184]

However, not only infective agents are associated with increased morbidity and mortality, as has previously been described; it has also been hypothesized that an impaired or inappropriate modulation of Toll-like receptors (TLRs), which are involved in the recognition of invading microorganisms, and in the defense of the host following natural infections, could exert a critical role in the development of autoimmune conditions.[185]

Overall, influenza vaccines are very safe[186] and well tolerated in most age-groups and formulations. Admittedly, they can cause AEs and/or rare AEs, some of which are more prevalent in children, while others are more prevalent in adults. However, symptoms due to AEs, such as rhinorrhea or congested nose, are usually transient. Severe allergic reactions to influenza vaccines are very rare, being estimated at less than 1 in a million doses.[187]

Another critical factor is that the currently available influenza vaccines are not well suited for use in low and middle-income countries (LMIC),[188] the health systems of which often lack the resources to implement vaccination adequately. Indeed, the WHO standards concerning the programmatic suitability of vaccines are not met by many influenza vaccines in LMICs. In these conditions, the priority target group is that of young children (< 5 years), whereas other risk groups are considered secondary targets.[189]

Further studies of all influenza vaccines, involving follow-up periods to bring to light possible increases in hospitalization, should be conducted on children < 2 years, children from LMICs or children with prior asthma or wheezing. It is necessary that safety tests be conducted in this age group, for which data regarding AEs upon LAIV administration are currently insufficient.

Vaccines have to meet higher safety standards, since they are administered to healthy people, mainly healthy children.[8] The monitoring of annual influenza vaccine safety, which is particular important on account of the annual changes in the viral antigen composition of the vaccine, constitutes a critical component of the influenza vaccination program. Indeed, not only does this strategy ensure the safety of vaccines, it can also maintain public trust in the national vaccination program. However, it must be borne in mind that no vaccine is 100% safe in all subjects, that vaccines may potentially cause AEs, and that the safety profile of a given pandemic influenza vaccine may not be completely described.[3,80]

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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