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Review

The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper☆,☆☆

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ABSTRACT

Most influenza vaccines are generally safe, but influenza vaccines can cause rare serious adverse events. Some adverse events, such as fever and febrile seizures, are more common in children than adults. There can be differences in the safety of vaccines in different populations due to underlying differences in genetic predisposition to the adverse event. Live attenuated vaccines have not been studied adequately in children under 2 years of age to determine the risks of adverse events; more studies are needed to address this and several other priority safety issues with all influenza vaccines in children. All vaccines intended for use in children require safety testing in the target age group, especially in young children. Safety of one influenza vaccine in children should not be extrapolated to assumed safety of all influenza vaccines in children. The low rates of adverse events from influenza vaccines should not be a deterrent to the use of influenza vaccines because of the overwhelming evidence of the burden of disease due to influenza in children.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; ADEM, acute disseminated encephalomyelitis; AE, adverse events; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory neuropathy; AS03, an adjuvant containing squalene, DL-α-tocopherol, and polysorbate 80; CDC, Centers for Disease Control and Prevention (US); CI, confidence intervals; CISA, Clinical Immunization Safety Assessment; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computerized tomography; DTaP, diphtheria, tetanus, acellular pertussis vaccine; DTwP, diphtheria, tetanus, and whole cell pertussis vaccines; EAE, experimental autoimmune encephalomyelitis; ECDC, European Centre for Disease Prevention and Control; EMA, European Medicines Agency; FS, febrile seizures; GACVS, Global Advisory Committee on Vaccine Safety; GBS, Guillain-Barré syndrome; HA, hemagglutinin; HAI, hemagglutination inhibition; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IIV, inactivated influenza vaccine; IRR, incidence rate ratios; ITP, immune thrombocytopenia; LAIV, live attenuated influenza vaccine; LAIV-L, live attenuated influenza vaccine – leningrad strain; MF59, an adjuvant containing squalene, polyoxyethylene sorbitan monooleate (Tween™ 80) and sorbitan trioleate; MMR, measles mumps rubella vaccine; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSL, Multiple Sleep Latency Test; NACI, National Advisory Committee on Immunization (Canada); OR, odds ratio; ORS, oculorespiratory syndrome; PCR, polymerase chain reaction; PCV13, pneumococcal conjugate vaccine-13 valent; PRISM, FDAPostlicensure Rapid Immunization Safety Monitoring; QIV, quadrivalent (inactivated) influenza vaccine; RI, relative incidence; RR, relative risk; SCCS, self-controlled case series; TIV, trivalent (inactivated) influenza vaccine; TM, transverse myelitis; VAERS, vaccine adverse event reporting system; VAESCO, Vaccine Adverse Events Surveillance and Communications Consortium; VSD, Vaccine Safety Datalink.

☆☆ *Disclaimer*: The findings and views expressed in this white paper are those of the authors alone and do not necessarily reflect those of Johns Hopkins University or of the World Health Organization.

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1. Executive summary

Vaccines to prevent influenza have been administered to hundreds of millions of individuals throughout the world during the past 70 years and use of influenza vaccines is increasing in many areas. The purpose of this review is to summarize the available published English-language literature on the safety of influenza vaccines in children to assist decision-making regarding recommendations for use of these vaccines in children. The review does not include information regarding the burden of disease, vaccine effectiveness, cost, cost-effectiveness, supply, delivery and other factors that are included in decision-making regarding the use of vaccines. Influenza results in severe disease including pneumonia and other complications, hospitalization, and mortality in all age groups. Children, especially young children, are at increased risk of complications. The benefits from influenza vaccines, including prevention of the enormous burden of influenza disease, far outweigh the risks of adverse events summarized in this review.

Our literature searches identified 15,878 published articles about influenza vaccine safety for screening; 6001 were found to have information of potential value in the assessment of causal relationships between influenza vaccines and adverse events. For many of the adverse events reviewed, case reports based only on temporal associations have not provided valuable information regarding causal assessments and only a few are referenced in this review to illustrate specific points. Data from controlled clinical trials, population-based epidemiologic studies, and studies that provide objective data on biologic mechanistic evidence have been selectively included because these studies provided stronger evidence than temporal associations only in case reports, case series, or reports from passive surveillance of adverse events.

We identified 108 influenza vaccines with unique names produced in the past decade in 27 countries by 47 manufacturers (Appendix 3). Some of these vaccines may be the same products marketed under different names, but we were unable to identify duplicates from the published literature and other online sources. Types of influenza vaccines recently produced include live and inactivated, monovalent, bivalent, trivalent, or quadrivalent preparations, whole virion, split-virus (with or without adjuvants), surface antigen, and virosomal. Influenza vaccines based on new production methods may result in different safety profiles. Caution is needed when drawing general conclusions about all influenza vaccines based on studies of only one or a few vaccines because there have been differences in the safety profiles of the many different vaccine available.

Influenza vaccines produced in recent years in Europe and North America are much safer for children than vaccines produced 30–40 years ago due to improvements in production methods. Some unexpected adverse events causally associated with inactivated influenza vaccines have been attributed to differences in production methods; for examples, see sections on febrile seizures, oculorespiratory syndrome, and narcolepsy. Some past safety problems could be repeated and/or new safety problems could occur as new manufacturers undertake the preparation of influenza vaccines. This review does not include a systematic review of differences in vaccine production methods.

In 2003, the Global Advisory Committee on Vaccine Safety (GACVS) recognized the need for robust post-licensure vaccine safety monitoring in all countries. Experiences with influenza vaccines reinforce this need as important differences in vaccine safety have been observed in different countries. Given the limited resources to conduct large population-based studies of vaccine safety in many countries, there is a need for enhanced global vaccine safety monitoring and cooperation between countries by sharing data in a timely manner to address safety questions. In 2013, GACVS published a manual for review of individual reports of adverse events, but only briefly mentioned criteria for assessing general causality on a population basis. Comprehensive review and detailed criteria for general causality assessment is needed on a population level. More effort is needed to define what evidence is sufficient to conclude that there is no increased risk of adverse events associated with vaccines, and the precise language used to report causality conclusions to avoid misunderstandings should be refined. Revised criteria for assessing general causality are proposed in this white paper (see Section 3.2).

Most influenza vaccines are very safe and the great majority of individuals receiving these vaccines have minimal side effects that are generally mild and self-limited. The most common adverse events reported after injectable inactivated influenza vaccines are local reactions and/or mild systemic reactions. Rare instances of large local reactions that resemble cellulitis occur for unexplained reasons. Most adjuvants are associated with increased rates of local reactions and some may be associated with increased rates of fever and other systemic reactions.

Fever was very common in young children following whole-virus influenza vaccines produced several decades ago, and febrile seizures occurred at unacceptable rates. Adverse events with these vaccines were dose related. Information on rates of fever and febrile seizures in young children is limited to only a few of the many modern vaccines that have been recently produced. Improvements in vaccine production methods have resulted in some split-virus vaccines that induce little or no fever when administered alone. Some currently available split-virus or virosomal vaccines are associated with minimal or no increased rates of adverse events at full adult doses as compared to half-doses in children 6–35 months of age. Simultaneous administration of one influenza vaccine (Fluzone) with pneumococcal conjugate (and possibly DTaP) has resulted in increased rates of fever and febrile seizures. Additional studies are needed with other vaccine preparations. One inactivated split-virus influenza vaccine produced in Australia resulted in unusually high rates of fever and febrile seizures in 2010 and is no longer recommended for use in young children in several countries, but this vaccine is in use for older children and adults. Differences in the methods used for viral disruption and changes in viral strains selected for vaccine production resulted in viral particles that appear to have caused the high rates of fever and febrile seizures. This experience indicates the need for continued monitoring of vaccine safety in children even when no substantial changes in manufacturing process are introduced as well as a careful review of production methods for all influenza vaccines that might be used in children.

Modern whole-virus vaccines are generally more immunogenic than equivalent doses of split-virus vaccines and appear to be well tolerated by adults. In the small numbers of children studied, the adverse event rates are higher following whole-virus vaccines than with split-virus vaccines. Larger trials of inactivated whole-virus vaccines need to be performed in children to better define the risks of fever, febrile seizures and other severe adverse events.

Hypersensitivity, or allergic reactions, occur following both live and inactivated influenza vaccines; anaphylaxis occurs at a rate of approximately one per million doses. Milder allergic reactions, including urticaria and respiratory symptoms, occur more commonly. Some allergic reactions have been due to residual egg protein from the manufacturing process, but there are other allergens in these vaccines that may be responsible for some allergic reactions. Changes in manufacturing processes have resulted in vaccines with only trace amounts of residual egg protein that can be safely administered to people who have allergy to eggs. Several new vaccines have been developed that do not use eggs in the manufacturing process but allergic reactions have been reported following these products; at the time of this writing, none have been approved for use in children. Oculorespiratory syndrome (ORS) is a disorder

that resembles allergic reactions, but is not due to an IgE antibody mediated process. Changes in manufacturing processes to reduce aggregations of viral proteins have resulted in significant decreases in the risk of ORS.

Influenza vaccines have been associated with some other serious adverse events. Vaccines produced in 1976 resulted in an increased risk of Guillain-Barré syndrome (GBS) in adults at a rate of approximately 1 in 100,000. Pandemic 2009 H1N1 vaccines were associated with an increased risk of GBS in adults at a rate of 1–3 per million within the six weeks following immunization. The incidence of GBS increases with age, and there is insufficient evidence to determine if there is an increased risk of GBS in children following any influenza vaccine.

In 2000–2001, an intranasally administered inactivated influenza vaccine containing an *Escherichia coli* heat-labile toxin adjuvant caused Bell's palsy, apparently from toxin mediated local inflammatory changes. Neither live nor inactivated influenza vaccines recently in use have been shown to cause Bell's palsy.

Two pandemic 2009–10 H1N1 influenza vaccines (produced by the same manufacturer) were associated with increased risks of narcolepsy in several countries. Underlying genetic predisposition to narcolepsy explains some of the variability noted in different countries. The biologic mechanism for the increased risk has not been completely determined but differences in vaccine antigens and/or the AS03 adjuvant may partially explain the association. Other influenza vaccines did not result in any increased risk of narcolepsy. The evidence is unclear regarding the possible increased risk of narcolepsy following infection with the pandemic H1N1 influenza virus. Although a possible increase in diagnosed narcolepsy was noted in one area of China associated with infection by the pandemic 2009 H1N1 influenza virus, other countries have not reported any increased risk in spite of widespread infections.

The available evidence does not establish a causal relationship between influenza vaccines and acute disseminated encephalomyelitis (ADEM) or transverse myelitis, but the available evidence cannot rule out the possibility of a small increased risk following influenza vaccines. If there is any risk following influenza vaccines, this risk is very low.

Although each epidemiological study of associations between influenza vaccines and multiple sclerosis (MS) reported to date has had relatively low power to rule out an increased risk, these studies as a group provide consistent evidence against a causal association with MS onset or relapse and influenza vaccine in adults. Studies are more limited in children, due in part to the lower risk of disease, but there is no signal to indicate evidence of concern.

There is no increased risk of immune thrombocytopenia (ITP) or inflammatory arthritis associated with influenza vaccines. However, incorrect injection of influenza vaccines too high in the deltoid muscle can cause acute and chronic bursitis as well as inflammation in the shoulder joint and head of the humerus.

Intranasally administered live attenuated influenza vaccines based on the Ann Arbor parent virus (LAIV) and the Leningrad based live vaccine (LAIV-L) produce transient rhinorrhea and congestion. Both vaccines are associated with a small increase in the risk of low-grade fever in young children and a possible increased rate of high fever in less than 1% of children. One study indicated that children 18–35 months of age in the United States with a past history of wheezing had an increased risk of wheezing following LAIV, but a study in Bangladesh with LAIV-L found no increase in wheezing in children with or without a past history of wheezing. One study in children under one year of age indicated an increased rate of wheezing in all children following LAIV and a possible increased rate of hospitalization from all causes in the 6 months following vaccination. Additional safety data are needed before these live vaccines are licensed for use in children younger than 24 months of age.

In summary, influenza vaccines are generally very safe in adults and several influenza vaccines have been shown to be very safe in children, but influenza vaccines can cause rare serious adverse events. There are differences in susceptibility to adverse events by age. Some adverse events, such as fever (and associated febrile seizures), are more common in children than adults, while other adverse events occur more commonly in adults. Safety data for children in English-language publications are available for only a small number of the influenza vaccines that are being produced. Safety studies including enough participants to detect known or possible adverse events identified following other vaccines should be conducted in the age groups of intended users,. There can be differences in the safety of vaccines in different populations due to underlying differences in genetic predisposition to the adverse event (Table 1).

2. Introduction

The purpose of this review is to provide information on the safety of influenza vaccines administered to children to assist decision-making regarding immunization of children. The review does not include information regarding the burden of disease, vaccine effectiveness, cost, cost effectiveness, supply, delivery and other factors that are included in decision-making regarding the use of vaccines. Influenza results in severe disease including pneumonia and other complications, hospitalization, and mortality in all age groups. Children, especially young children, are at increased risk for complications [1]. Influenza vaccines can prevent much of the large burden of disease caused by influenza; the benefits from vaccination far outweigh the risks of adverse events summarized in this review.

We have conducted a systematic review of the available English-language peer-reviewed literature on influenza vaccine safety using comprehensive search terms to identify all relevant articles and objective and reproducible methods to systematically review these publications. However, new articles are being published daily and some important publications may be in non-English language literature. Also, we do not have access to unpublished information that manufacturers or investigators may have generated. We have attempted to be thorough in our search for information about influenza vaccine safety, but any such effort may miss some articles. We have not included all references identified for all adverse events studied because the list would be very long. In some reviews, we have chosen representative articles to illustrate key points or identify the range of adverse event rates associated with influenza vaccines in children. We have not tried to make a comprehensive list of all theoretical concerns that have been raised. There is insufficient time and space to review all such concerns and undoubtedly new ones will rise in the future.

3. Systematic approach to reviews

Adverse events were selected for review if there was evidence of possible causal relationships with one or more influenza vaccines included in guidelines for the use of influenza vaccines, package inserts, reviews by the Institute of Medicine (IOM), published reviews on influenza vaccine safety, and a literature review for vaccine safety and influenza vaccines. Recently produced vaccines were identified from the WHO, the WHO Prequalified Vaccines website (http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/), searches of websites for regulatory authorities including the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and manufacturers identified through Google searches. The list of vaccines (Appendix 3) includes information from the WHO table of pandemic and seasonal influenza vaccines accessed October 30, 2014, but the WHO

Table 1
Adverse events associated with one or more influenza vaccines.

Adverse event	Age group at risk	Estimated risk[a]	Vaccines	Comment	Risk from natural disease
Local reactions	All	Very common	All IIV	Higher rates with adjuvanted	None
Severe		Rare			
Shoulder injury/bursitis	Primarily adults	Very rare	All IIV	Often due to incorrect injection	None
Myalgia	All	Common	All		Very common
Fever (Febrile seizures)[b]	Children (0.5–5 yrs)	Very common (Rare)	Higher rates with simultaneous PCV vaccine	Variable rates by vaccine	Very common
Hypersensitivity (Anaphylaxis)	All (All)	Rare (~1/million)	All		None
Oculorespiratory syndrome	All	Rare	Some IIV	Variable rates	None
Guillain-Barré syndrome	Adults	Very rare	H1N1 IIV	Rates increase with age	Very rare, but higher than from vaccines
	Children	Uncertain	Probable all IIV		
Narcolepsy	Adults	Uncertain	Only with 2 vaccines[a]	Rates vary by genetic predisposition	Uncertain
	Children	Very rare			
Rhinorrhea and Congestion	Primarily children	Common	LAIV only		Very common
Wheezing	Under 2 yrs	Common	LAIV only		Very common

[a] CIOMS descriptions: Very common >10%; Common (frequent) >1% to <10%; Uncommon (infrequent) >0.1% to <1%; Rare >0.01% and <0.1%; Very rare <0.01% [11].
[b] More severe/rare forms of AE and rates noted in parenthesis.

table does not include comprehensive information on approved ages for administration, virus strains or name of the vaccine. When information was found for the same vaccine produced in different years, only information for the most recently produced vaccine was included. Links to package inserts and manufacturers of the vaccines were included when was available.

3.1. Literature reviews

The search terms for the primary reviews of individual adverse events are included in Appendix 1. PubMed and EMBASE databases were searched separately for each adverse event category. A third database, Scopus, was searched for GBS and febrile seizures, but was then removed from the search protocol due to overlap with EMBASE results. Search terms were edited for greater accuracy as we refined the search process. Within each search, results were filtered to exclude articles not available in English as well as comments, editorials, letters, news and notes. When appropriate, searches were further filtered to exclude articles not pertaining to humans and, in topics for which there were ample studies, we limited our focus to children. The numbers of published articles returned for each search was recorded and reported in Appendix 2. Publications were sorted by types and separated by review articles, case reports, conference materials and clinical trials to allow for prioritization of data extraction. Clinical trials were given highest preference, followed by epidemiologic studies, and publications in reviews. Case reports or conference materials were extracted when there was lack of epidemiologic and/or biological mechanism data. Some individual case reports were referenced in some reviews to highlight specific issues and/or to illustrate the logic used by authors for concluding that diseases were causally related to one or more influenza vaccines. Studies utilizing inappropriate epidemiological or statistical methods were not included. Search results were exported to EndNote, and duplicate articles were deleted. The remaining articles were screened by the primary authors for each section for relevance and chosen for data extraction. Additional articles that provided insight into biological mechanisms of adverse events were selectively identified during this screening process. Selective additional searches were conducted in PubMed to help address specific questions that were identified during the reviews. The search results are limited to articles available from PubMed or EMBASE as of September 30 and/or early October 2014 that included search terms in the title, abstract or index categories. Examples of relevant articles missed by our Narcolepsy search are 'Harris 2014', which had no abstract or indexing available and did not include "influenza" or an equivalent term in the title. Also missed was the European Centre for Disease Prevention and Control (ECDC) Technical Report entitled, "Narcolepsy in association with pandemic influenza vaccination: A multi-country European epidemiological investigation", which was available at http://www.ecdc.europa.eu/ but not from PubMed or EMBASE. As each adverse event section was reviewed, some additional brief literature reviews were conducted in order to identify possible pathogenic mechanisms and evidence for biologic plausibility for possible causal associations with influenza vaccines. Also, outside expert reviewers provided some supplemental information and references, including review articles, and specific studies on biological mechanisms that were relevant to the assessment of causal relationships.

3.2. Assessment of casual associations

For this review, the following criteria have been accepted as evidence of a causal relationship: (1) evidence of an increased risk in vaccine recipients as compared to controls; or (2) evidence of an increased risk in biologically plausible time windows as compared to control windows in self-controlled studies; or (3) local reactions at the site of the injection when there is no evidence of other possible causes such as other vaccines administered at the same site or trauma; or (4) with live attenuated vaccines, evidence of the vaccine virus or bacterium confirmed by genetic sequencing in the affected tissue of patients with a serious adverse event can sometimes establish a causal relationship even with a single case report [3]; or (5) immediate hypersensitivity reactions occurring within 4 h after immunization when there is no evidence of other possible exposures that could have resulted in a hypersensitivity reaction. Other illnesses with longer time intervals that can mimic immediate hypersensitivity reactions require epidemiologic evidence to support a causal relationship.

The WHO Global Advisory Committee on Vaccine Safety (GACVS) has published guidelines for assessment of causality for vaccine safety (http://www.who.int/vaccine_safety/initiative/investigation/New_aide_mem_causal_assmt.pdf?ua=1). In 2013,

GACVS published a manual with revised guidelines for review of individual adverse events and assessment of causal associations of these cases [4,5]. The manual includes a brief outline of criteria for assessing causality on a population basis, but there is a need for a comprehensive review of the assessment of causality on a population basis and to establish criteria for concluding that there is no increased risk of specific adverse events associated with vaccines. Robust vaccine safety studies are capable of detecting small increases in risk that do not meet previous strength of association criteria. Also, the old criteria for specificity are outdated. Recent studies have identified small increases in risk of adverse events associated with vaccines that are also caused by other factors, such as febrile seizures and GBS. Self-controlled studies can preclude the need for comparisons of vaccinated persons with unvaccinated individuals. The investigations of narcolepsy associated with the AS03-adjuvanted pandemic H1N1 vaccine have shown that plausibility based upon existing knowledge is not essential for determining a true causal relationship.

The strongest evidence for causality assessment comes from placebo-controlled randomized trials. However, the relatively small sample sizes often result in inadequate power to detect or rule out rare adverse events. Also, the limited duration of follow-up in most clinical trials limits the ability to detect adverse events with vague timing of onset and adverse events with long intervals between vaccine receipt and symptom onset. Retrospective cohort, case–control and self-controlled case series studies provide high quality evidence when conducted properly. Self-controlled and case-only studies where the vaccine recipients or persons with a disorder serve as their own controls have emerged to be one of the most useful epidemiologic methods for assessing vaccine safety [6]. These studies provide evidence for or against an increased risk in biologically plausible time windows without the need for comparisons with unvaccinated or control populations. Self-controlled studies eliminate many potential biases and problems associated with identification of appropriate controls in case–control studies and comparison populations in retrospective cohort studies.

Before concluding that an adverse event is causally related to a vaccine, most experts require evidence from multiple studies in different populations by different investigators, sometimes using different study methods. However, there can be true differences in the rates of adverse events in different populations due to differences in genetic or environmental factors that might influence the risk of developing the adverse event. Some adverse events have been identified in selected populations at increased risk, but the adverse event is not observed in other populations.

Establishing a biologic mechanism alone is sometimes accepted for determining a causal relationship such as anaphylaxis and isolation of a live vaccine agent in tissues or body fluids affected by the adverse event [3]. A thorough discussion of the assessment of biologic mechanisms can be found in the 2012 report from the Committee to Review Adverse Effects of Vaccines of the Institute of Medicine ([7], pp. 57–101). An understanding of the biologic mechanism is not essential to determining a causal association when there are convincing epidemiologic data establishing an increased risk of the adverse event in vaccine recipients. Animal studies can provide useful information with regard to the pathogenesis of adverse events, but there also are examples where studies in animals have led to false conclusions with regard to effects in humans [8]. Animal studies have provided valuable insight into the pathogenesis of adverse events following vaccines after epidemiological studies have established an increased risk of the adverse event in humans [9]. Mechanistic evidence in the reviews of individual adverse events is included when the evidence helps explain the pathogenesis. For most adverse events associated with influenza vaccines, epidemiological evidence has proven to be the primary evidence establishing or ruling out causal relationships.

Repeat challenge is a valuable tool for the assessment of causal relationships for immediate hypersensitivity reactions, but care must be taken to be certain that the challenge does not result in nonspecific reactions that can mimic the local reactions associated with hypersensitivity reactions [10]. For other types of adverse events, repeat challenge can provide some evidence supporting a causal association, but most reports do not fulfill the criteria established by the IOM including reasonable latency for each event in the same individual following the same vaccine, documentation of vaccine receipt, and clinician diagnosis of the health outcome [7].

Reviews of adverse events were sought for evidence of causal associations with influenza vaccines, but conclusions from these reviews were not used for determining causal relationships in this white paper. The IOM has reviewed evidence of causal associations between influenza vaccines and adverse events [7]. This committee started from a neutral position and weighed the evidence for or against a causal relationship. For 23 of the 27 adverse events evaluated, the committee concluded that "The evidence is inadequate to accept or reject the causal relationship. . ." ([7], pp. 402–404). These conclusions have limited value in helping public health experts and clinicians with decision-making. Also, these conclusions are sometimes misunderstood as there is evidence supporting a causal relationship, but the evidence is "inadequate". For example, the IOM reviewed three large studies where the investigators were unable to find any cases of encephalitis or encephalopathy following influenza vaccines, and concluded that "no conclusions could be drawn from these analyses" ([7], p. 296). The absence of identified cases in biologically plausible time windows following influenza vaccines in active surveillance programs where all health outcomes are captured in large populations provides evidence against a causal association, and if there is a possible causal association, the absolute risk of the specific adverse event must be very small.

When precise rates of adverse events were not identified, we followed the Council for International Organizations of Medical Sciences (CIOMS) guidelines for describing rates of adverse drug reactions [11]. Briefly, the guidelines use the following categories: Very common >10%, Common (frequent) >1% and <10%, Uncommon (infrequent) >0.1% and <1%, Rare >0.01% and <0.1%, Very rare <0.01%.

Case reports based on temporal relationships only do not contribute to the assessment of causal relationships. However, there is some value to assessment of reports from passive surveillance systems even when there is no control or comparison group. Some information from these reports is included in the reviews of a few adverse events that follow.

3.2.1. *Causal association with one or all vaccines*

There are reports of adverse events after only one or some influenza vaccines but the evidence is not available for all influenza vaccines. Some adverse events have been reported only with historical vaccines. Changes in vaccine production have reduced or eliminated these adverse events. Limited information is included in this review about such adverse events because we were asked to focus on currently available vaccines, although new manufacturers could produce vaccines that might result in repeat experiences with these adverse events.

3.2.2. *Age*

Some adverse events that are causally associated with influenza vaccines occur only or primarily in adults, and some occur more frequently or only in children. Whenever possible, we have tried to provide data on possible causal associations and rates of adverse events that have been causally associated in children. In instances where the data on safety have been generated primarily in adults, we have provided an assessment of the likelihood that the adult data are applicable to the pediatric population.

3.3. Adverse events associated with injection technique

We have included a review of deltoid or subacromial bursitis which is associated with inappropriate injection techniques because this is a preventable and relatively common adverse event and the evidence is strong for a causal relationship. We are not including information about other adverse events that may be associated with programmatic errors, such as contamination of multi-dose vials and inappropriate reuse of needles and syringes.

4. Influenza vaccines recently produced

Information was obtained on 133 vaccines that have been produced recently. After deleting entries that did not contain information on type of vaccine, 108 vaccines were identified produced by 47 manufacturers in 27 countries (Appendix 3). The numbers of different types of influenza vaccines produced per manufacturer ranged from one to 15. Of the 59 seasonal influenza vaccines (tri- and quadrivalent), 34 are approved for persons younger than 18 years; of the 63 H1N1 pandemic vaccines, 15 were approved for persons younger than 18 years of age. None of the pre-pandemic H5N1 vaccines have been approved for pediatric populations. Of the 108 vaccines, 98 were inactivated and 10 were live vaccines; 7 vaccines were quadrivalent.

This list does not include non-English language information and some manufacturers' websites included neither prescribing information nor contact information; other manufacturers did not have a web presence that we could identify. Difficulty distinguishing unique vaccines arises when manufacturers sell vaccines in multiple countries. For example, Abbot has employees and operations in more than 130 countries, Baxter in 44, and GSK in 32. Some companies distribute the same vaccine under different brand names in different countries and some manufacturers have production plants in more than one country, or they manufacture in one country and distribute the vaccine in other countries. The manufacturer country on the list refers to the country identified in the package insert (or equivalent) as the place of manufacture. The list includes a few vaccines that are not currently available such as some vaccines in clinical phase 3 trials and some vaccines that are in stockpiles for pandemic situations [12].

4.1. Whole-virus vaccines in children

Whole-virus inactivated vaccines were the mainstay of immunization against influenza from their development in 1945 until they were generally replaced with split-virus or subunit vaccines during the 1970s and 1980s, in large part due to the increased reactogenicity (see Section 5.4) [13]. In Hungary, an aluminum-adjuvanted whole-virus vaccine, Fluval, has been in use since 1997. Yearly licensing trials in adults have shown few adverse reactions [14]. In recent years, renewed interest in the increased immunogenicity of whole-virus vaccines has led to the development of new whole-virus pandemic vaccines.

A study of a Vero-cell derived whole-virus inactivated pandemic 2009 H1N1 vaccine compared 2 doses of either 3.75 μg or 7.5 μg of vaccine (Celvapan, Baxter) in 341 children 6 months to 17 years of age in Austria and Germany without a placebo arm [15]. Temperatures were monitored for 7 days after vaccine administration; other adverse events were monitored for 21 days after each vaccination. Fever assessed to be related to vaccine was not reported in children 9–17 years old, but occurred in 5.9% of children 1–8 years old and 18.8% of children 6–11 months. Most fevers were 38–39 °C, no febrile convulsions occurred. Other systemic reactions (irritability, sleep disorder, headache, fatigue, muscle pain, etc.) occurred in 14.3% or less of children 1–17 years old, and 16.7–50% of infants 6–11 months of age. Injection site reactions occurred in less than 20% of children of all ages and tended to be reported more commonly in the older children. Another study in the UK assessed Vero cell-culture derived whole-virus H1N1 vaccine (Baxter) vs. an $AS03_B$ adjuvanted H1N1 split-virus vaccine (GlaxoSmithKline) in 943 children 6 months to 12 years [16]. The adjuvanted vaccine was more reactogenic and more immunogenic than the whole-virus vaccine, mirroring what was seen in a similar trial in adults [17]. After either the first or second dose, 1.1% of whole-virus vaccine recipients over 5 years of age had severe local reactions [16]. In children 6 months to <5 years, 9.3% of first dose recipients and 12.5% of second dose recipients had fever ≥38 °C, whereas children 5–12 years had lower fever rates (3.3% after first dose, 2.9% after second). One child who received the whole-virus vaccine had a focal seizure, but it was assessed as unrelated to the vaccine. In addition to fever, children 6 months to 5 years of age who received the whole-virus vaccine experienced the following adverse events after the first and second vaccination in rates higher than 20%: redness after vaccination (22.9% and 19.2% after first and second doses); decreased feeding (33.7% and 29.9%); increased irritability (35.5% and 28.4%) and need for analgesics or antipyretics (27.6% and 23.6%). Children over 5 years experienced higher rates of pain at the injection site (39.8% after first dose, 42.3% after the second), redness at the injections site (22.7% and 21.7%), generally feeling unwell (24.9% and 14.9%) and headache (33.7% and 26.3%) [16].

In India, an aluminum-adjuvanted whole-virus monovalent H1N1 vaccine was tested in 2010 at 10 mcg or 15 mcg single doses in children and adults 3–76 years of age [18]. Adverse events were not reported separately for children and adults. Of the 161 recipients of the 10 mcg dose, and the 157 recipients of the 15 mcg dose, less than 1% developed a fever. 13.7% and 18.5% had pain at the injection site, the most frequently reported adverse event. Headache was reported in 6.8% of 10 mcg recipients and 4.5% in those who received 15 mcg of the adjuvanted vaccine. The reported reactogenicity events were generally mild and of short duration [18]. In a large placebo-controlled trial in China, eight formulations of the H1N1 vaccine (varying doses of split-virus, whole-virus, adjuvanted and unadjuvanted) were tested in 12,691 people 3 years and older in a 2-dose regimen [19]. Children received only the split-virus regimen (with or without aluminum adjuvant). Adults received split-virus and whole-virus vaccines. The whole-virus vaccines were given at 5 mcg and 10 mcg doses and were adjuvanted with aluminum. Adverse events in adults reported after the whole-virus vaccines (in 9.5% of those who received 5 mcg and 11.8% who received 10 mcg) were comparable to those experienced by adults who received placebo or 15 mcg or 30 mcg of the unadjuvanted split-virus vaccine (9.6%, 10.2% and 12.4%), and were less than those experienced by those receiving the adjuvanted vaccine (17.5–23.3%) [19].

Whole-virus vaccines for potential future avian pandemic influenza strains have been developed because inactivated H5N1 subvirion vaccines were poorly immunogenic without an adjuvant [20]. Attempts to make an immunogenic inactivated H5N1 vaccine have included adjuvants, vectored vaccines, and a prime-boost strategy with two different vaccines. One trial involving 675 children 6 months to 17 years of age using 3 doses of 2 different unadjuvanted Vero cell derived whole-virus H5N1 vaccines was conducted in Finland, Australia, Spain and Singapore in 2009–2012 [21]. Children 6 months to 8 years were given either 3.75 mcg or 7.5 mcg doses, those 9–17 years were given 7.5 mcg. After the first dose, injection site reactions, mostly mild in nature, occurred in 19.4–32% of the children, with older children reporting more reactions, mostly pain. Fever in the 7 days after vaccination occurred primarily in the younger children: 3.5% of children 3–17 years experienced fever compared to 18.1% of those 6–35 months. Headache, at 18.7%, was the most common systemic complaint in those 9–17 years old. Irritability was the most common systemic symptom in

the youngest children, occurring in 22.2% of those of 6–35 months. Fever rates were lower in the second and booster immunizations. Other approaches to whole-virus H5N1 vaccines are being developed. In Hungary, a whole-virus H5N1 vaccine (Fluval) was tested in 12 children ages 9–17 years with no side effects reported [14]. An aluminum hydroxide adjuvanted clade 2.2 vaccine was shown to be well tolerated in 80 adults in Russia [22]. Vietnam is developing capacity to produce pandemic avian influenza whole-virus vaccines [23].

4.1.1. Summary

In summary, modern whole-virus vaccines are more immunogenic than equivalent doses of split-virus vaccines and appear to be well tolerated by adults. In the small numbers of children studied, the adverse event rates are higher than with split-virus vaccines. Larger trials of inactivated whole-virus vaccines need to be performed, especially in children, in order to determine the risks of febrile seizures and other severe adverse events.

5. Evidence for or against causal relationships between influenza vaccines and adverse events

5.1. Local reactions following IIV

Most inactivated influenza vaccines are given by intramuscular injection. An intradermal formulation available for use in adults only will not be reviewed here. In clinical trials the reported rates of pain, tenderness, swelling have ranged from a low of 0.0% [24] to 50–60% [25], but most studies have reported intermediate rates of 10–20% following vaccines without adjuvants. The wide variability in the reported rates of local adverse reactions can be attributed primarily to differences in the methods of data collection.

The most reliable data come from blinded clinical trials comparing influenza vaccines with a placebo, or one vaccine with another using daily monitoring of signs and symptoms. In direct comparisons, inactivated vaccines induce higher rates of local reactions than placebo [26,27]. TIV preparations produced using cell culture technology have induced local reactions that are similar to egg-based vaccines [25]. In recent years, most studies have compared standard seasonal influenza vaccines with monovalent pandemic vaccines or adjuvanted pandemic or pre-pandemic vaccines. Most local adverse events are mild and transient [26,27]. However, some local reactions can interfere with daily activities and rare instances of extensive local reactions that resemble cellulitis have been reported following several different vaccines (see below). In adults, the rates of reported pain have been higher in females than males [28].

Dose

The rates of local reactions following several TIV preparations were not increased by giving the standard 0.5 mL dose administered to adults and older children as compared to the 0.25 mL dose that has been recommended for children 6–35 months of age [29].

Adjuvants

In direct comparisons, vaccines containing AS03 or MF59 adjuvants induced higher rates of pain/tenderness, erythema, induration, and swelling in most studies in adults and children than vaccines without an adjuvant [30–33,379–381]. Local reactions increased with increasing amounts of adjuvant for most adjuvants. No consistent differences were noted between the first and second dose for young children. Almost all of these reactions were mild or moderate in severity and the vaccines were considered to be well tolerated.

5.2. Cellulitis-like reactions

Inactivated influenza vaccines and other vaccines can induce reactions that can be mistaken for bacterial cellulitis [34]. The median time following immunization to onset is approximately one day [34]. Duration is 1–3 days in most instances. In a review of medical claims, no increased rate of claims was noted in the seven days following influenza vaccine for cellulitis, but an increase in claims for cellulitis was detected following pneumococcal polysaccharide vaccines [35]. Many affected individuals are treated with antibiotics. The vast majority of such reactions are not local infections however cellulitis due to bacteria can occur, possibly associated with contamination of multi-dose vials [36]. Criteria are needed to help clinicians distinguish between cellulitis caused by bacterial infections and cellulitis-like reactions due to vaccines. The pathogenesis of cellulitis-like reactions has not yet been determined, but is presumed to be a form of delayed type hypersensitivity reaction.

Other

For reasons that have not been determined, in children with primary varicella infections, the skin lesions may be preferentially localized to the injection site for influenza or other vaccines [37].

5.3. Hypersensitivity reactions

Hypersensitivity reactions to drugs and biologicals are characterized by WHO as dose-independent, unpredictable, noxious, and unintended [38]. Hypersensitivity reactions can be immune mediated or mediated through other mechanisms (non-immune mediated).

5.3.1. Immune mediated reactions

Most immune-mediated hypersensitivity reactions are allergic reactions mediated by IgE antibodies and result in urticaria (hives), generalized pruritus, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms, and/or cardiovascular collapse. A severe, life-threatening generalized or systemic hypersensitivity reaction is considered to be anaphylaxis [39] although more specific criteria have been proposed and the presentation in infants is different than for older children and adults [40]. Prior exposure to the allergen can generate IgE antibodies that attach to basophils and mast cells. Re-exposure to the allergen results in degranulation and release of a variety of inflammatory mediators including histamine [41]. IgE-mediated reactions generally occur within an hour after exposure, but later reactions have been described [42].

An estimated 1.6% of the adult population in the United States has had an episode of anaphylaxis following exposure to foods, drugs, insect stings, latex, and other environmental allergens [43]. Vaccines represent a very small proportion of the allergens responsible for allergic reactions. Influenza vaccines contain several potential allergens that could result in allergic reactions, including residual proteins from the media used to produce the vaccine (egg protein or ovalbumin), small amounts of residual antibiotics (polymyxin B or neomycin), stabilizers (gelatin), or preservatives (thiomersal) [43–45]. Some influenza vaccines have latex in the vial stoppers and/or the plunger of prefilled syringes; the latex can cause allergic reactions in highly sensitized latex allergic patients [46]. Egg allergy has been assumed to be responsible for many of the immediate hypersensitivity reactions to influenza vaccines and for many years advisory committees considered egg allergy to be a contraindication or precaution for administering influenza vaccines (earlier recommendations 1980s to 2000). Variable amounts of residual egg protein were found in different influenza vaccines in

the early 2000s [47]. Some manufacturers introduced additional filtering steps in manufacturing of vaccines used in the United States resulting in reduced amounts of residual egg protein [48]. Most egg-allergic individuals can safely receive influenza vaccines produced in egg because the very small amount of egg protein is insufficient to trigger an allergic response [49–51]. In recent years, two vaccines (Flucelvax® manufactured by Novartis and FluBlok® by Protein Sciences Corporation) have been approved that are produced using recombinant technology without the use of eggs, but these products are currently only approved for use in persons 18–49 years of age. The ACIP has recommended that persons 18–49 years of age who have had allergic reactions to eggs should receive these recombinant vaccines [50]. Younger individuals who have had only hives after ingestion of eggs can safely receive any of the other egg-based vaccines. Children who have had more serious allergic reactions after ingestion of eggs can receive egg-based vaccines administered by a physician experienced in the management of severe allergic conditions. Specific information on the amount of egg protein content is not available for most influenza vaccines.

Components other than egg protein appear to be responsible for some of the immediate hypersensitivity reactions following influenza vaccines as children with such reactions have been identified who have no evidence of egg allergy. In Canada, a case–control study revealed several risk factors for anaphylaxis following an AS03-adjuvanted 2009 pandemic H1N1 vaccine: female gender, a prior acute respiratory infection, drug allergy, or food allergy (but not egg), vaccination during the first 4 weeks of the campaign, and use of asthma inhalers [52].

The majority of patients who have had signs or symptoms of hypersensitivity reactions following vaccines probably do not have IgE mediated disease [53]. In Canada, skin testing was performed on 95 individuals 10–64 years of age who reported allergic symptoms after receipt of the pandemic 2009 H1N1 vaccine that contained the AS03 adjuvant and the results were compared to 37 controls [54]. All of the cases had onset of symptoms less than 24 h after receipt of the vaccine, and 52% were within 1 h after vaccination. Positive skin tests to the vaccine they received indicating probable IgE antibody mediated reactions were obtained in 4% of the cases and 3% of the controls. Of the 25 cases who agreed to be revaccinated with the 2011–12 influenza vaccine, five (20%) had delayed onset allergic type reactions. The authors concluded that IgE mediated allergy was responsible for very few of the reported allergic symptoms following influenza vaccination.

Urticaria, angioedema and other manifestations of hypersensitivity can also occur at intervals of up to one week after exposure to allergens. These late reactions are likely mediated by IgG or IgM antibody, and/or complement and are characterized as serum-sickness reactions [55]. Most such reactions are hives/urticaria but angioedema can occur as well. Although there are many reports of delayed onset rashes following influenza vaccines with a presumption of a causal relationship, we have not identified studies that provided evidence of such causal relationships. In these instances, it is very difficult to determine a causal relationship because of the potential for other exposures, such as food and other allergens as well as inter-current viral illnesses in the interval between vaccine receipt and onset of disease.

5.3.2. Non-immune or non-allergy mediated hypersensitivity reactions

Hypersensitivity reactions can be mediated through non-immune mechanisms. Some products can interact directly with mast cells and/or basophils to release histamine and cause adverse events that can mimic immune mediated adverse events [53,56]. These adverse reactions have been called “anaphylactoid” reactions, but many allergists now prefer to refer to these as “non-allergy mediated hypersensitivity reactions”.

The term ‘oculorespiratory syndrome’ (ORS) was first used in Canada to describe patients who developed bilateral red eyes and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing/throat tightness, hoarseness or sore throat) and/or facial swelling beginning within 24 h after influenza immunization [57–60]. Most affected patients had resolution of symptoms within 48 h, but up to 10% had symptoms that lasted as long as a week. ORS occurred in all age groups, including children 1–19 years of age, although the rates were higher in individuals over 50 years of age. The rate in females was higher than males with a ratio of approximately 3:1. ORS is not IgE antibody mediated. Skin testing of ORS patients with influenza vaccines was negative for immediate reactions. ORS was associated with two vaccines, but 96% of cases in one year were associated with vaccine that was produced using deoxycholate for virion disruption, and this vaccine was found to contain increased amounts of unsplit virus and aggregations of virus products [58,61]. In a retrospective survey of children with diabetes, the rate of ORS in children vaccinated in 2000 was as high, and possibly higher, than the rates reported for adults [60]. The rate among first-time vaccine recipients was higher than for children who had received influenza vaccine in the previous season. Approximately 1% of children who developed ORS were hospitalized with this condition, primarily children with respiratory symptoms. Changes in manufacturing processes decreased the amount of aggregated virus and decreased rates of ORS over a 4-year period from 46 per 100,000 to 9 per 100,000 doses distributed [58]. Some patients with ORS following influenza vaccine are reported each year in Canada in recent years, but the rates are considerably lower than observed in 2000–2004 (Personal communication Gaston DeSerres, September 24, 2014). Reports of patients with onset of facial swelling and/or other signs of ORS with onset 4–24 h after influenza vaccines have been identified in the United States in recent years [62].

Revaccination of patients with ORS resulted in recurrences in 34% of recipients of one vaccine and 15% who had received a different vaccine [57]. The recurrences were usually mild and there was no increased risk of anaphylaxis or other forms of immediate hypersensitivity reactions. The pathogenic mechanisms responsible for ORS have not been determined, but aggregation of viral particles appears to have been a key factor with one vaccine. Revaccination of affected individuals who did not have severe lower respiratory symptoms is considered safe by advisory committees [50,63,326].

Evidence for a causal relationship

The incidence of immediate hypersensitivity reactions is usually too low to be picked up in clinical trials. Negative data from randomized clinical trials involving relatively small numbers of study participants does not rule out a causal association for uncommon or rare adverse events [64].

Individuals who have developed immediate hypersensitivity reactions within minutes following influenza vaccine have had evidence of hypersensitivity on skin testing to the vaccine or a vaccine component, supporting a causal relationship [43]. Additional evidence supporting a causal relationship includes skin testing with diluted vaccines that induced characteristic wheel and flare reactions within minutes after the test was performed [43]. Studies of individuals who have had immediate hypersensitivity reactions have revealed elevated levels of serum IgE specific antibody, but the predictability of such test results is variable and repeat challenge, usually by skin testing, is considered a better approach to identifying hypersensitivity to specific allergens [65].

The rates of immediate hypersensitivity reactions vary based on differences in vaccine components, methods of manufacturing, the

populations who received the vaccines, and methods of reporting or investigating these events. In clinical trials involving hundreds or even a few thousand patients, it is uncommon to find patients who develop true immediate hypersensitivity reactions because the incidence is quite low. For example, in one recent trial of 915 children who received TIV, one child developed hives, but this child also received multiple other vaccines at the same time [66]. In most clinical trials no instances of immediate hypersensitivity reactions have been reported. Hypersensitivity reactions are reported through passive surveillance systems and can be among the most commonly reported adverse events [67]. For most seasonal vaccines rate data are not available. The introduction of 2009 H1N1 pandemic vaccines resulted in enhanced surveillance for adverse events and provided an opportunity to estimate the rates of serious allergic reactions because denominator data were available in many countries. Anaphylaxis is the most serious form of immediate hypersensitivity reactions and is probably the most reliably reported form of hypersensitivity. However, only 50% or less of the reports of anaphylaxis fulfilled the Brighton Collaboration criteria [62] Anaphylaxis meeting the Brighton criteria [68] was reported at a rate of approximately 1 case per million doses of the H1N1 2009 pandemic influenza vaccine distributed in the United States with no differences in rates for four manufacturers [62]. In Mexico, the rate of reported anaphylaxis was less than 0.5 per million doses administered for similar vaccines [69]. In Europe, 43 cases of anaphylaxis were reported following administration of approximately 12 million doses of an MF59 adjuvanted H1N1 2009 pandemic influenza vaccine for a rate of 3.5 per million doses distributed [70]. Also in Europe, the rate of anaphylaxis following AS03-adjuvanted vaccine was similar to the reporting rate for other vaccines [71]. In Quebec Canada, the rate of Brighton Collaboration confirmed anaphylaxis was 13 per million doses administered for an AS03-adjuvanted H1N1 2009 pandemic influenza vaccine, substantially higher than the rate reported for seasonal influenza vaccine [72]. In Korea, there were 5 cases of anaphylaxis and 10 anaphylactoid reactions reported among an estimated 13.8 million recipients of an unspecified adjuvanted vaccine [73].

In summary, anaphylaxis and other immediate hypersensitivity reactions have been reported for almost all influenza vaccines. Although there are differences in the rates of reported anaphylaxis in different countries and with different vaccines, the data are inconclusive with regard to true differences in rates by the type of vaccine.

The rates of less severe hypersensitivity reactions including hives/urticaria and/or angioedema have not been determined accurately because of underreporting and uncertain denominator data. For passive reports of adverse events following H1N1 influenza vaccine in the United States, the rate of other immediate hypersensitivity reactions reported to the Vaccine Adverse Events Reporting System (VAERS) system was approximately 10 times higher than the rate for anaphylaxis, but there was undoubtedly more underreporting of milder events. Allergists believe that the rate for these less severe hypersensitivity reactions is much higher than that for anaphylaxis and reporting rates are lower. The rates of all immediate hypersensitivity reaction were higher in females of reproductive age than in males in the United States [62]. Similarly, in Europe with the MF59-adjuvanted vaccine, the reporting rate for allergic reactions in females was more than twice as high as in males [70]. Anaphylaxis also has been reported following LAIV in children. Seven reports were made of anaphylaxis to VAERS after the first 2.5 million doses of LAIV were administered in the United States [74]. For the LAIV preparation of 2009 H1N1 pandemic influenza vaccine, the rates of all allergic reactions reported in the United States was higher than for the inactivated vaccines, but the rates of anaphylaxis were similar [62].

5.3.3. Other rash illnesses

There are case reports of other types of rash illnesses which could be due to delayed hypersensitivity reactions that had onset several days to two weeks after influenza vaccines without other recognized causes. These include unusual rashes such as Gianotti-Crosti syndrome [75], cutaneous vasculitis [76], toxic epidermal necrolysis [77] and Henoch-Schonlein purpura [78]. However, no evidence of a causal relationship, other than a temporal association, has been identified in these reports and coincidental infections or other exposures that could have stimulated these rashes or illnesses have not been ruled out in the published case reports. Most of the patients with these reported rashes and illnesses recover without sequelae.

5.4. Fever and febrile seizures

5.4.1. Fever

Fever in children is a common occurrence associated with infections, some vaccines, inflammatory diseases, heat stress, and other factors. The Brighton Collaboration Fever Working Group has defined fever to be "an endogenous elevation of at least one measured body temperature of $\geq$38 °C" [79]. Fever induced by inactivated or subunit vaccines is usually caused by direct effects of vaccine antigens and other components on macrophages and other cells which release inflammatory cytokines. Residual endotoxin from the vaccine production process can directly stimulate the release of inflammatory cytokines [80]. Fever from IIV and other inactivated vaccines has onset within the first 24 h but may occur up to 48 h after the vaccine has been administered [26,27,81]. With live attenuated vaccines, the interval from vaccination to onset of fever varies depending upon the replication time and incubation period associated with the live agent. For measles containing vaccines, the increase in fever is 7–10 days following vaccination [26,27,82].

5.4.2. Changes in influenza vaccine production methods

Influenza vaccines were rarely used in children prior to 1976 because of high rates of fever and other adverse events. Most vaccines were whole-virus vaccines and bacterial endotoxins were present in microgram quantities as a residual from bacterial contamination of eggs used for vaccine production [80]. However, the rates of fever in children were not directly correlated with the amount of endotoxin in the vaccines and investigators suspected that some viral components contributed to the high rates of fever [80]. Whole-virus vaccines induce fever in 45–69% of the small numbers of children studied, some had fever to 40 °C, and febrile seizures occurred in 3 of 42 children in two trials [81,83]. The rates of adverse events were lower with half the usual dose (0.25 mL) and with split-virion vaccines, which were first developed in 1969 (Fig. 1) [81,84–88]. The immunogenicity of the split-virus vaccine was less than the whole virion vaccines and so two doses were necessary in young children to induce an adequate immune response. In 1977, US advisory committees recommended influenza vaccine only for children at high risk for influenza complications and recommended that young children receive 2 doses of split-virus vaccines [89].

Additional changes in manufacturing processes for whole and split-virion inactivated vaccines have been made over the past 30 years which resulted in decreased rates of fever and local reactions, but most of these changes have not been outlined in the published literature. For example, allergists studied the amount of egg protein in influenza vaccines and noted that some manufacturers' products had much lower egg protein content than others, and the allergists sometimes selected the low egg protein content vaccines for immunizing people with possible egg allergy [48]. Additional filtration steps were introduced by other manufacturers, as acknowledged by two manufacturers at a meeting of the ACIP in

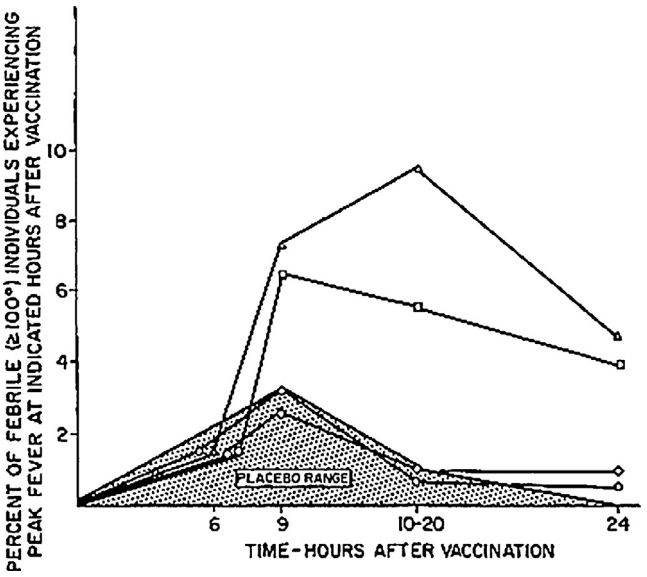

Fig. 1. Frequency of maximal fever at various times after vaccination with whole-virus (□, Merell-National Laboratories, Cincinnati, Ohio; and △, Merck Sharp and Dhome, West Point, Pa.) or split-virus (◊, Parke, Davis and Company, Detroit, Mich.; and ○, Wyeth Laboratories, Philadelphia, Pa.) influenza A/New Jersey/76 vaccine. Used by permission [85,86].

2011. The splitting agent used to disrupt the virus has changed in some instances (e.g. Vaxigrip®, Sanofi Pasteur) [90]. The specific details on manufacturing processes are considered proprietary. Therefore, caution is indicated when interpreting the results of studies of fever and local reactions between manufacturers, and data from earlier studies are not necessarily reflective of what reactions would occur with currently produced vaccines.

Studies of fever and febrile seizures in young children are available for only a small number of the vaccines produced. In many countries, IIV produced by only one manufacturer is approved for routine use in children under 3 years of age, the age group at highest risk for febrile seizures. Other IIVs are available in most countries for older children and adults (see Appendix 3).

5.4.3. Inconsistencies in study methods for assessing fever after vaccines

Inconsistencies in the study methods utilized by different investigators make it somewhat difficult to draw conclusions about differences in vaccines. Inactivated influenza vaccines have been associated with increased rates of fever in the 24–48 h after vaccination and some studies suggested a small increase in fever 24–72 h following LAIV [26,27]. Epidemiological studies and clinical trials have used longer time windows for reporting adverse reactions (5, 7, 10, 21, or 30 days after vaccination). However, these longer intervals often include fever and febrile seizures caused by other factors not biologically consistent with influenza vaccine. Studies have varied in the methods for measuring body temperature and cut-points for definitions of fever have included subjective fever reported by parents or caregivers. Influenza vaccines administered to children are often administered simultaneously with other vaccines that cause fever so it is not possible to determine which of the vaccines was responsible for fever. Also, simultaneous administration of other vaccines with influenza vaccine may increase the risk of fever and febrile seizures (see Section 5.4.5 below).

Fever occurs commonly in young children and, in the absence of an unvaccinated control group, it is not possible to determine a causal relationship with a vaccine. The Brighton Collaboration Fever Working Group developed guidelines for the gathering and reporting of fever in vaccine trials [79]. Few of the following trials meet these guidelines, in part because many were performed prior to their development.

5.4.4. Rates of fever after influenza vaccination

Rates of fever following influenza vaccines are highest in the youngest children and usually decrease with increasing age. In a summary of 7 clinical trials of different formulations of Vaxigrip® (Sanofi Pasteur) conducted between 1991 and 2002, the rates of fever in the first 3 days after vaccination among children 6–35 months of age were approximately twice the rate observed in children 3–10 years of age [90]. In other studies of split-virion vaccines in children 6–23 months or 6–35 months of age, fever in the 5 or 7 days after vaccination are usually in the 8–20% range and vary by the cut point for defining fever [91,92]. Some studies have found rates of only 4% [93,94], and one study reported rates of 1–3% in children 6–36 months of age using the same vaccines that had reported rates of 8–13% observed in other settings [382]. In general, fevers found after split-virus vaccines are low-grade, and rarely exceed 39 °C.

Fever rates in young children following split-virus vaccines without adjuvants do not correlate with immunogenicity. In studies of direct comparison of two different vaccines, similar rates of fever have been noted but one vaccine was more immunogenic than the other [93–95,382,383]. The fevers could have been caused by coincidental infections or there are factors in the vaccines that cause fever unrelated to the development of protective immune responses.

Quadrivalent inactivated influenza vaccines (QIV) produced by GSK (Fluarix®) and Sanofi Pasteur (Fluzone®) have been approved for use in children. Fluarix® QIV recipients had more injection site pain than the TIV preparation, but there was no significant difference in rates of fever [96]. As with TIV, after the receipt of QIV children 6 months to 3 years of age had higher rates of any fever than the older children and 2.5% had fever >39 °C after first and 5.4% after the second dose [97]. Fluzone QIV recipients did not have higher rates of fever than in the TIV recipients in children 6–23 months or 2 to <9 years of age in the 7 days after vaccination [98].

5.4.5. Fever associated with adjuvanted vaccines

Several manufacturers developed monovalent 2009 H1N1 split-virus pandemic vaccines containing adjuvants including aluminum, virosomes, and oil-in-water immersion adjuvants. In China, a comparison of a 2009 H1N1 split-virus vaccine with an aluminum adjuvant (Hualan Biological Bacterin Company) in 440 children 3–11 years old found fever in the 21 days after vaccination in 11.8% of placebo recipients and 11.5–18% who received 7.5–30 mcg HA of the adjuvanted vaccine [99]. Systemic adverse events were 13.6% in the 15 mcg HA group and 25.5% in the 30 mcg HA group. Some studies did not report safety data separately for aluminum adjuvanted vs. unadjuvanted vaccines or separate adults from children to allow interpretation of results [19]. In studies of an aluminum phosphate adjuvanted H5N1 prepandemic split-virus vaccine in children 6–35 months of age, fever (>37.5 °C) was noted in 48.3% of recipients of 30 mcg HA and 70% of those who received 45 mcg HA [100]. The rates were much lower in children over 3 years of age.

AS03 (squalene, DL-α-tocopherol, and polysorbate 80) is an adjuvant used in Pandemrix (GSK) in Europe and Arepanrix (GSK) in Canada. In persons over 18 years of age, rates of fever were minimal (1.3–4%) following the first or second doses of an H1N1 vaccines containing 3.75–15 mcg of vaccine with AS03 adjuvants [33]. In children, the rates of fever were higher after the second dose than the first dose. In 157 children 6–35 months of age studied in Spain, the rate of fever >37.5 °C was 20.2% after the first dose and 67.3% after the second dose in children who received the 1.9 mcg (0.25 mL) dose [101]. Higher fevers (>39.0 °C) occurred in 3.8% of

subjects receiving a second 0.25 mL dose, and in >15% of those who received the 0.5 mL dose [101]. A Canadian study in the same age group found rates of fever ≥38.5 °C of 3.6% and 8.6% after the first and second doses [384]. In a study in the UK, fever ≥38 °C occurred in 8.9% of 270 children 6 months to <5 years after the first dose and 22.4% after the second dose [16]. Fever rates were lower in older children, 20% in children 3 to <6 years old after the first dose of 1.9 mcg; 16.9% in children 10–17 years old after a second 3.75 mcg dose 6 months later [102,103].

MF59 (squalene, polyoxyethylene sorbitan monooleate (Tween™ 80) and sorbitan trioleate) adjuvant has been in Fluad® (Novartis) subunit seasonal vaccine since 1997 [104]. Focetria® (Novartis) is the European licensed egg-based pandemic H1N1 vaccine adjuvanted with MF59. Celtura® (Novartis) is the cell culture equivalent distributed in Japan, Europe and Latin America. In an integrated analysis of 5 trials involving 545 children conducted by Novartis, no differences in rates of fever were found in recipients of MF59 adjuvanted influenza vaccines as compared to unadjuvanted vaccines [105]. The overall rates of adverse events were lower in recipients of MF59 adjuvanted vaccines. Fever rates after the second dose of MF59 adjuvanted vaccines were either similar to or lower than the rates after the first dose in several studies [30,106–109,385]. The rates of fever in children who were born preterm were similar to term infants [106]. Fever (usually ≥38.0 °C) rates varied by study, but were similar to or slightly higher than the rates following licensed unadjuvanted vaccines in several studies of children 6–35 months of age in different countries including Finland [30], the United States [107] Guatemala [385] and Argentina, Australia, Chile, the Philippines, and South Africa [109].

A pandemic monovalent H1N1 vaccine adjuvanted with AF03, another squalene-in-water emulsion (Sanofi-Pasteur) was compared to unadjuvanted vaccine in 303 children ages 3–17 years and 401 age 6–35 months in Finland [31]. Fever rates in the 7 days after vaccination were higher in the younger children: for infants 6–11 months 41.3% of those who received the adjuvanted vaccine had temperature ≥38 °C compared to 13.7% in the unadjuvanted group. Fever rates were 25% in 12–23 month old recipients of the adjuvanted vaccine, and 17% in those 24–35 months of age [31].

5.4.6. Increased fever with simultaneous pneumococcal conjugate vaccines

Studies of children 6–35 months of age who received TIV with pneumococcal conjugate vaccine showed higher rates of fever than when TIV was administered alone [92,110,386].

5.4.7. Febrile seizures

Fever predisposes to seizures in a small percent of children and the risk of seizures increases with increasing temperatures. Febrile seizures are defined as seizures which occur in febrile children (≥38 °C from any source) without evidence of intracranial infection, metabolic disturbances, or history of afebrile seizures [111,112]. Febrile seizures are age-dependent and are most common in children 6 months to 2 years of age, but occur up to 5 years of age [111]. The cumulative risk of developing one or more febrile seizures in the first 5 years of life varies from 2 to 5% of children in North America and Europe to 6–9% in some Asian countries [113,114]. The risk of developing one or more febrile seizures has not been clearly defined in children in many other areas of the world. Risk factors associated with developing febrile seizures include high fever, infections, some immunizations, low birth weight, and family history of seizures [114,115]. Children who develop febrile seizures differ from children who have not developed febrile seizures in specific genetic loci associated with control of pro-inflammatory cytokine interleukin 1β (IL-1β) and they develop increased levels of IL-6 [116].

Febrile seizures can be categorized as simple or complex. Simple febrile seizures last less than 10 min as defined in the United Kingdom, and 15 min in the United States, occur once in a 24-h period, and are generalized (non-focal) [111,114]. Although simple febrile seizures are generally benign, they are a source of significant concern and distress to families. Complex febrile seizures last longer than 15 min, can occur more than once in 24 h, and may have a focal component [111]. There are no long-term adverse effects of simple febrile seizures [111]. However, a small proportion of children can develop recurrent febrile seizures, and a subset may be at higher risk for developing epilepsy [111,117]. Febrile seizures may also unmask a predisposition to seizures. Studies in the Netherlands have shown that 65% of children who go on to have additional seizures have an underlying disease that is associated with recurrent seizures or other neurologic problems [118]. Complex febrile seizures have a higher risk of recurrent febrile seizures and future afebrile seizures, and prolonged febrile seizures can be associated with neurologic damage.

Most seizures in young children are witnessed only by parents and criteria for defining seizures and possible seizure-like activity have not been included in most studies. The Brighton Collaboration has developed definitions for seizures, including febrile seizures, which should help standardize methods for future studies [119].

Although there were numerous reports of febrile seizures after influenza vaccine to passive reporting systems such as VAERS in the US, no conclusions can be drawn with regard to causal relationships; many of these reports included children who received other vaccines simultaneously [120–122]. However, passive reports can provide a signal that warrants further investigation as occurred with a vaccine in Australia discussed below.

Epidemiologic studies using the Vaccine Safety Datalink (VSD) in the US and self-controlled analyses in children and risk windows of 14 or 21 days after vaccination found no evidence of increased risk of febrile seizures [123,124]. Most seizures occurred 7–14 days after TIV administration and were thought to be due to concomitant MMR vaccination. In a case–control study of febrile seizures using insurance group enrollees 6–34 months of age from 2002 to 2004, the hazard ratio for FS associated with TIV was 1.17 (95% CI 0.36–3.86) [125]. A later study in the VSD using a self-controlled study design over 4 influenza seasons (2002–2006), revealed a small increased risk of medically attended fever in 66,283 children 24–59 months of age (IRR 1.71; 95% CI 1.64–1.80), but no serious adverse events were observed and there was no mention of FS [126].

5.4.8. Febrile seizures after pandemic (H1N1) 2009 vaccine

Several prelicensure studies involving relatively small numbers of young children did not show an increased risk of FS including trials of adjuvanted vaccines Arepanrix® and Pandemrix ® [93,94,109,127]. However, a signal of increased febrile seizures was seen in post-marketing surveillance in Australia in 2010. The Department of Health in the state of Western Australia had offered TIV to children 6 months to 4 years old since 2008. In 2010, three TIV vaccines were distributed: Fluvax® and Fluvax Junior® (CSL Biotherapies), Influvac® (Solvay Pharmaceuticals) and Vaxigrip® (Sanofi Pasteur). All contained A/California/7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus and B/Brisbane/60/2008-like virus. The program was suspended 3 weeks into the campaign when clinicians noted an increase in children presenting with fever, vomiting, and febrile convulsions within 12 h of TIV vaccination [128–130]. A retrospective cohort analysis revealed a significant ($p < 0.001$) increase in febrile seizures in 2010 (see Fig. 2) [128].

Elevated risk of febrile convulsions was associated with two vaccines (Fluvax® and Fluvax Junior®) produced by CSL Biotherapies in children under 5 years of age, but not the other manufacturers. No febrile seizures were reported in recipients of Influvac®, compared

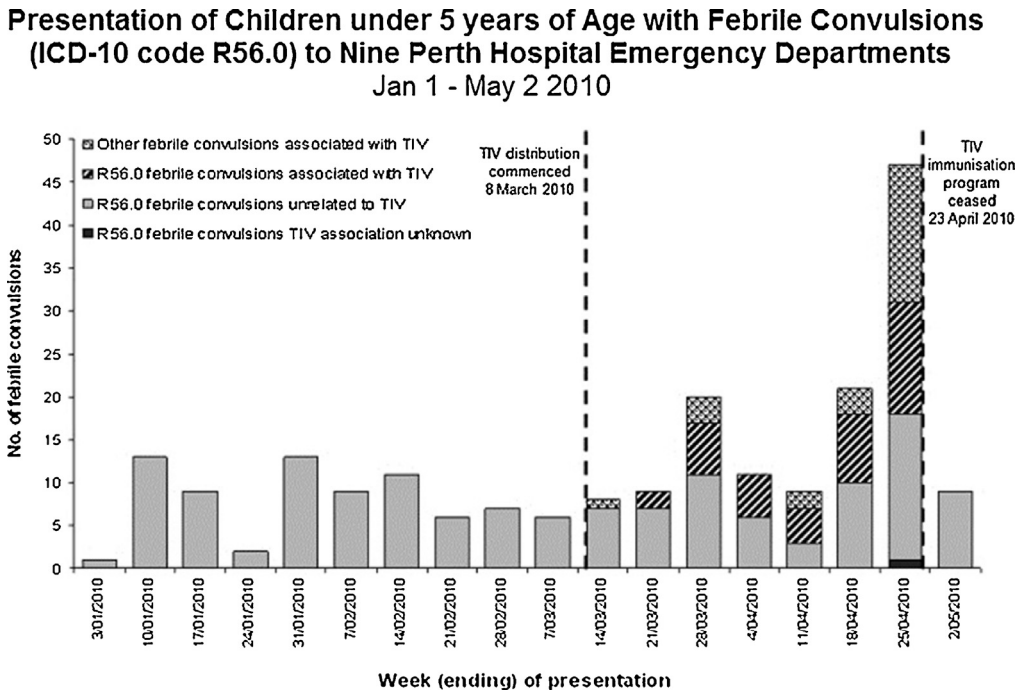

Fig. 2. Used by permission [128].

to a rate of 4.4 per 1000 doses administered (95% CI 3.4–5.6) for the CSL products ($p < 0.0001$). The rate of other fever related reactions was 14.8 (95% CI 8.3–26.7) times greater for the CSL products than for Influvac®. Prior vaccination with TIV or monovalent 2009 H1N1 pandemic vaccine was not associated with febrile convulsions [128]. CSL's influenza vaccines are no longer recommended for children <5 years in Australia, and recommended only for children 9 years of age and older in the United States [50]. Similarly, the Department Of Health in the United Kingdom recommended not using either of the two CSL produced influenza vaccines (Enzira® or CSL Biotherapies generic influenza vaccine marketed by Pfizer) in children [131].

Previous published trials did not indicate safety concerns with the CSL products. A randomized trial of monovalent unadjuvanted 2009 H1N1 vaccine produced by CSL administered to 370 patients 6 months to <9 years old in Australia reported one febrile convulsion in an 18 month old 20 days after vaccination who had concurrent pneumonia [132]. Surveillance data in Australia of monovalent H1N1 non-adjuvanted vaccine (Panvax® and Panvax Junior®, CSL), included more than 300,000 doses of Panvax Junior® in children <5 years. Seven febrile seizures were reported in the first six months of the vaccination program, two of which occurred with concomitant varicella vaccine, below the expected background rate convulsions in children <5 years of age cited in the package insert [133]. In addition, a prospective uncontrolled phase IV clinical trial of CSL TIV vaccine was conducted in Australia in 2009, to evaluate safety of Fluvax® and Fluvax Junior® in children 6 months to 18 year of age. Among 1992 participants, fever was more common than a 2009–2010 Northern Hemisphere split-virion comparator, but no febrile seizures were discussed [134].

There was a suggestion of increased reactogenicity in previous studies. An Australian study of Fluvax® in 2005–2006 reported fever in 22% of children under 3 years in 2005, and 40% after a second dose in 2006, with one febrile convulsion [135]. In New Zealand, retrospective telephone surveys of parents of children 6 months to 5 years revealed that fever occurred more frequently with Fluvax® compared to Vaxigrip® (Relative Risk 4.33 [95% CI 2.44–7.70], $p \leq 0.001$). The authors concluded that similar to previous studies, Fluvax® was more pyrogenic in infants and young children [136]. Citing unpublished studies, investigators noted that there was evidence for higher rates of fever and possibly febrile seizures associated with the CSL products prior to 2010 [137]. They also identified a possible publication bias and called for standardization in the methods used to identify and report fever associated with influenza vaccines in children. In 5 published trials, the median average weekly risk of fever was 8.2% (range 5.3–28.3%) in children from 6 months to <36 months of age following influenza vaccines, significantly ($p = 0.04$) lower than the rate (26.0% (range10.3–70.0%)) in 14 unpublished trials [137].

In an effort to understand increased rates of FS and other adverse events associated with the CSL products, the manufacturer conducted studies in several animal species, including nonhuman primates, which did not reveal any differences between the CSL products and other manufacturers with regard to detectable adverse events [138]. However, studies with peripheral blood from both children and adults revealed significant increases in stimulation of cytokines and chemokines after stimulation with the CSL products as compared to other manufacturer's products. Further studies demonstrated that the increase cytokine and chemokine reactions were due to heat labile viral derived fragments and a viral lipid-mediated delivery of fragmented RNA [139,140]. Inadequate splitting of the vaccine virions by the sodium taurodeoxycholate used in manufacturing these products associated with changes in the virus strains resulted in the differences in reactivity. By introducing additional steps in the manufacturing process to further disrupt virions and remove lipid, the manufacturer hopes to be able to develop a product that would be satisfactory for use in children [139–141]. Other manufacturers use deoxycholate in the manufacture of influenza vaccines, including the manufacturer of influenza vaccine that was most strongly associated with ORS (see section on ORS below) [142]). The high rates of ORS reduced with the introduction of additional steps to assure adequate viral disruption in the production of split-virus vaccines.

Several countries, including China, Denmark, Slovenia, the Netherlands, and the UK published results of passive surveillance systems in the context of the 2009 H1N1 pandemic, most receiving monovalent vaccine. Although some febrile convulsions were

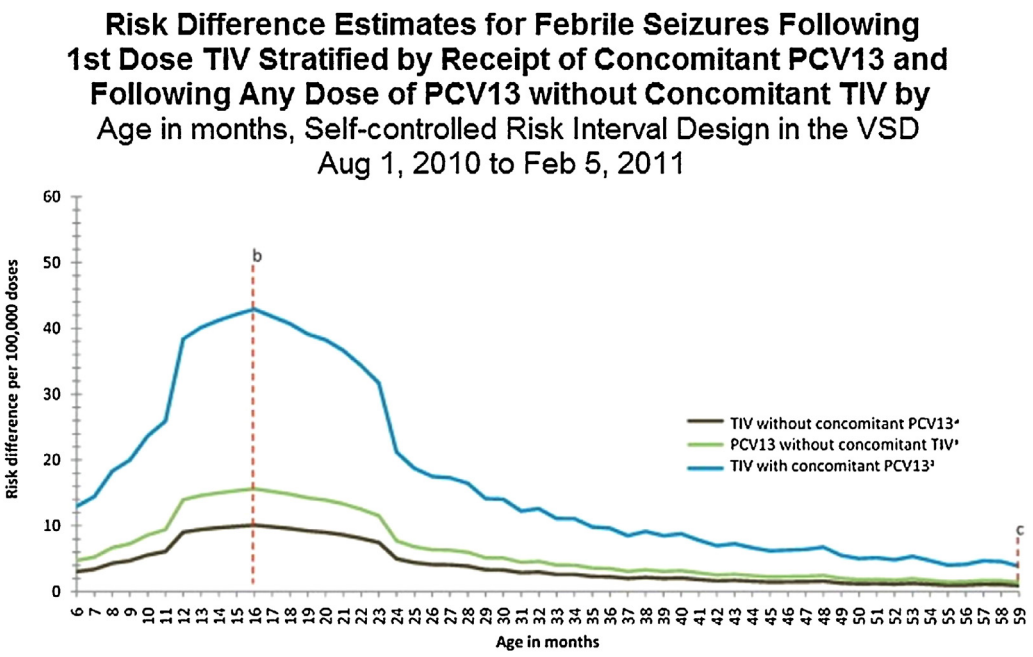

Fig. 3. Used by permission [149,150].

reported, no strong signals or increased risk of FS with TIV among children were noted [143–147].

5.4.9. Increased febrile seizures with simultaneous pneumococcal conjugate vaccines

Following the identification of FS associated with the CSL vaccine, many countries enhanced vaccine safety monitoring. In the United States, enhanced surveillance of VAERS from 2010 to 2011 identified 51 reports of FS after Fluzone® TIV (Sanofi Pasteur) in children <2 years of age, which exceeded a predetermined threshold [148]. VSD data for 2010–2011 showed the risk for FS among children 6 months to 5 years was highest for those receiving concurrent pneumococcal conjugate vaccine (PCV13) and TIV [149,150]. Using a self-controlled method, the incidence of FS that met Brighton Collaboration criteria in the 0–1 days after vaccination was compared to the incidence in the 14–20 days after vaccination. The results shown in Fig. 3 revealed a small increased risk associated with TIV alone or PCV 13 alone, but a much larger increase in risk when both vaccines were administered simultaneously. There was an elevated risk in all the ages studied, but the risk was greatest in children 6–24 months of age. At 16 months of age, the risk difference was 12.5 per 100,000 doses for TIV without PCV13, 13.7 per 100,000 doses for PCV13 without TIV, and 44.9 per 100,000 doses for TIV and PCV13.

In a follow-up study using VSD data from 2006 to 2011 in children 6–23 months of age, 333 FS were identified [151]. The analysis confirmed the increased rate of FS with simultaneous administration of PCV 13 and influenza vaccine, but also showed that concomitant administration of TIV, PCV13, and DTaP was associated with the highest risk of FS, which was observed for all influenza seasons. A separate study using different methods to assess the risk of FS among participants in a health plan during the 2010–2011 season revealed elevated point estimates of risk of FS, but no statistically significant increased risk associated with TIV, PCV13, or administration of both vaccines on the same day [152]. Post marketing surveillance of TIV in Canada among 592 children 6–59 months old in 2010 indicated fever was more likely with concurrent administration of PCV13, although no seizures were reported [153]. Studies evaluating co-administration of LAIV with other vaccines, including MMR, varicella vaccine, and oral polio vaccine, have not shown increased risk of FS [154,343].

Overall, at least 19 different vaccines by 10 different manufacturers have been evaluated for fever and/or FS (Appendix 4). Given lack of direct comparisons between manufacturers, aside from the risks associated with CSL Fluvax discussed above, it is difficult to determine if the relative risk of FS differs by manufacturer; the overall risk of FS was low across most manufacturers. The risk of FS can vary by manufacturing method and perhaps by vaccine strain. Studies with sufficient power to determine the rates febrile seizures have only been published recently for a relatively small number of manufacturers. Trials done to date with newer influenza vaccines, such as quadrivalent (QIV) and thiomersal-free formulations, have not shown increased risk of FS [96–98,373]. A prospective study to evaluate the safety of a monovalent cell culture-derived influenza vaccine reported two convulsions, both outside the 7-day risk window generally associated with vaccine effects [155].

5.4.10. Febrile seizures following LAIV

No increased risk of FS has been reported for LAIV. In a post marketing evaluation of VAERS reports for the 2003–2005 seasons, approximately 2.5 million people received LAIV and only 460 AE were reported during the study period including one febrile seizure reported in a 4 year-old boy 26 h after LAIV [74]. An analysis of the VAERS data from 2005 to 2012 revealed 2619 reports of AE following LAIV, 15 of which were seizures, 2 reported as febrile [156]. The authors did not believe that this was an increase above what was expected by chance. A randomized controlled trial comparing LAIV [157] to TIV (Fluzone®) in 2004–2005 among 8352 children 6–59 months of age at sites across the US, Europe, Middle East, and Asia, reported one episode of FS in the TIV group and none in LAIV group [158]. In addition, an analysis of AE associated with LAIV in the 2007–2010 seasons using MarketScan insurance data, noted 1 seizure among children younger than 5 years [159,160].

5.4.11. Conclusions

With improvements in manufacturing processes, febrile seizures in children receiving IIV have become relatively rare. With improved study methods including narrowing risk windows and focusing on the age groups at highest risk for FS, large population-based studies have revealed a small increased risk associated with IIV, especially with simultaneous administration of PCV13 and

with DTaP. The experience with the use of LAIV in children is more limited. LAIV is not recommended for children younger than two years of age so there are only limited data from pre-licensure studies on the risk of fever and FS in the population at highest risk of FS. Additional data from large studies using LAIV and LAIV-L are needed to determine if there is any increased risk of FS associated with these vaccines.

Experience with the increased rate of FS with vaccines produced by CSL indicates the need for careful monitoring of vaccine safety on an ongoing basis in all countries and studies to help understand the biologic basis for fever and FS, as well as the possibility of developing vaccines by new methods that might be associated with even lower risks [141].

5.5. Malaise, myalgia, and related symptoms

Reports of myalgia, malaise, chills and a sensation of fever after IIV have been reported in adults and are often the most common symptoms reported [17,161,162]. Some people have reported these symptoms as a "flu-like" illness [26,27,163,164] and these symptoms have resulted in refusal of subsequent influenza vaccinations.

The onset of these symptoms is higher in the first day after vaccination and may persist into the second day, but many studies have combined data for the 7 or 10 days after vaccination. These symptoms are nonspecific and there is a relatively high background rate in actively solicited symptoms among adults. Higher rates of apparent influenza-like illness symptoms have been reported among vaccine recipients vs. controls especially in the first 2 days after vaccination in some studies [163,164], but not in others [163–165]. Higher rates of myalgia were reported in recipients of high dose as compared to standard dose vaccines [166].

The rates of myalgia were similar for adult recipients of split-virion unadjuvanted TIV vs. QIV (14.3% vs. 16.2% respectively) in the 7 days after vaccination [167]. The rates were significantly higher in the same study for recipients of AS03-adjuvanted vaccines: 31.4% for TIV and 38.5% for QIV. Similar results were found in a comparison of whole virion pandemic H1N1 vaccine where the rate was 24% for unadjuvanted recipients and 49% for recipients of AS03 adjuvanted vaccine [17].

In children, these symptoms following influenza or other vaccines are usually mild and, since they do not often result in medical visits, they are not generally reported in population-based studies of medically attended events [126,168]. Myalgia comprised 6% of non-serious adverse events after TIV in children in an analysis of VAERS reports in children 5–17 years of age from 1990 to 2006 [122]. Active follow-up in pediatric clinical trials shows a greater incidence of malaise and myalgia after vaccination. Myalgia and malaise were the most commonly reported systemic symptoms and occurred in more than 30% of children 2–8 of age who received QIV or TIV (Fluzone, Sanofi Pasteur) [98]. Myalgia occurred in approximately 30% of children 5–17 years of age in the 3 days after vaccination following two different TIV formulations (Fluzone, Sanofi and Fluarix GlaxoSmithKline) [95]. Other studies have reported rates of 4% to >30% in children old enough to verbalize complaints [96,97,135,169,170]. These symptoms usually started within the first 24 h after receipt of the vaccine.

5.5.1. Pathogenesis

Myalgia and malaise are associated with influenza infection and the pathogenesis involves viral replication and the systemic inflammatory response [171,172]. Myalgia and malaise after influenza vaccination arise in the absence of viral infection and are most likely related to the increase in inflammatory cytokines and a decrease in IL-8 that occurs shortly after vaccination [173–177] (Talaat unpublished). A better understanding of the role of cytokines play in the adverse events following immunization is needed.

5.6. Inflammatory arthritis

Juvenile idiopathic arthritis (JIA), formerly called juvenile rheumatoid arthritis, is a chronic and often relapsing autoimmune inflammatory arthritis in children with onset before the age of 16 years [178]. JIA includes seropositive rheumatoid arthritis as well as chronic arthritis in children with other predisposing risk factors but, in the majority of cases, there is lack of serum IgM-rheumatoid factor, lack of family history, and no known underlying etiology [179]. Environmental factors, especially infections, are suspected to be either trigger factors or contributing factors in the pathogenesis of JIA [180–182]. The association of transient arthralgia and inflammatory arthritis with several different acute infections and live attenuated rubella vaccines has led to the hypothesis that other live and inactivated vaccines could cause or trigger the onset of JIA in genetically predisposed individuals or stimulate exacerbations of quiescent disease. No known association exists between natural influenza infection and the onset or exacerbation of JIA or other inflammatory arthritides to support a causal relationship between influenza vaccine and inflammatory arthritis.

Case reports

There are rare case reports of children with onset or relapses of JIA following IIV [183], and other reports of onset of inflammatory arthritis in adults following influenza vaccines with assumptions of causal relationships based upon temporal associations [184–186].

Epidemiologic evidence of associations between influenza vaccines and exacerbation or new onset of JIA in children or rheumatoid arthritis in adults

In 2012, the IOM concluded that the few studies [187,188] of associations between influenza vaccines and onset or exacerbation of arthropathy were limited and did not have sufficiently standardized measures of disease severity or definitions to allow for an assessment of causal relationships; the IOM concluded that the evidence was "inadequate to accept or reject a causal relationship" ([7], p. 385). More recent studies have included objective measures of disease assessment. Clinical trials in patients with JIA and other forms of autoimmune inflammatory arthritis have consistently revealed no evidence of increases in relapse rates or changes in disease severity for patients with JIA and other forms of inflammatory arthritis following IIV with or without adjuvants [189–195].

In an exploratory cohort analysis using the VSD population in the United States, a possible increased risk of rheumatoid arthritis was found in persons 15–59 years of age using time windows of 180 and 365 days following immunization (RR = 1.36, $p = 0.03$; RR = 1.34, $p = 0.01$), but not in the more biologically plausible 90 days following immunization [196]. In the same study using a case–control methodology, there was no evidence of an increased likelihood of having received influenza vaccine or other vaccines in any of the time windows prior to onset of disease in 378 cases of new onset rheumatoid arthritis.

A retrospective cohort study involving all persons residing in Stockholm County, Sweden, using data from January 1, 1998 through August 31, 2010, revealed no evidence of any increased risk of inflammatory arthritis associated with the AS03 adjuvanted Pandemic (H1N1) 2009 vaccine immunization campaign [197]. In a matched retrospective cohort study involving children 5–17 years of age and using data from influenza seasons 2003–4 through 2007–8 seasons in the US-based VSD, no evidence of increased rates of inflammatory arthritis was found in 43,702 who received LAIV or their matched IIV recipients as compared to controls [198]. In a population-based case–control study in Sweden involving 1998 incident cases of rheumatoid arthritis from 1996 to 2006 in persons 18–70 years of age, no evidence of any association with

receipt of influenza vaccine or other vaccines was noted (OR 1.0, 95% CI: 0.9–1.1) [199].

Summary and conclusions

Although there are some case reports of onset or relapses of JIA following administration of influenza vaccine, the evidence from multiple epidemiologic studies indicates that influenza vaccines are not risk factors for new onset of JIA in children or inflammatory arthritis in adults, and there is no association with exacerbation of symptoms in patients with JIA.

5.6.1. Subacromial or deltoid bursitis and shoulder injury

Injection of influenza and other vaccines too high in the deltoid muscle can result in inflammation of the subacromial bursa associated with persistent pain and restriction of range of motion [200–203]. The onset of significant shoulder pain is usually within hours after injection, increases for several days and persists for several weeks to months. Clinically, differentiation from brachial neuritis and adhesive capsulitis (frozen shoulder) can be difficult [201,204]. Magnetic resonance imaging (MRI) reveals inflammation and extra fluid collection in the subacromial bursa which extends to above the humorous [201,202]. There are also rare reports of inflammatory changes in the head of the humorous with osteonecrosis or osteolysis associated with subacromial bursitis following injection of standard influenza vaccine and one report following an AS03 adjuvanted H1N1 influenza vaccine [202,205,387]. The cases of subacromial bursitis reported to date appear primarily in adults. Contributing factors include injection too high in the deltoid, injection at an upward angle, and small or thin deltoid muscles.

These injuries can be prevented by injection of influenza vaccine into the middle third of the deltoid [28,201,206,207].

5.7. Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an immune-mediated disorder in which an antigenic stimulus results in an aberrant immunologic response that attacks self-proteins on peripheral nerve and nerve roots. GBS is divided into subgroups based on neurologic findings and neurophysiological characteristics, and includes acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory neuropathy (AMSAN), acute sensory neuropathy, acute pan-dysautonomia and the Fisher syndrome [208]. Pathologic findings vary for the subgroups, but inflammatory macrophages and/or antibodies against self-proteins attacking neuronal tissue at different points is a common feature [208]. Circulating antibodies play a role in the pathogenesis of most cases of GBS as evidenced by the rapid clinical response to the administration of large doses of intravenous immune globulin, which has become the standard of care. The passively administered antibodies presumably compete with and displace host anti-neuronal antibodies. The most likely candidate is anti-GM1 ganglioside antibody [209]. These studies have led to the hypothesis that, among the antecedent antigenic stimuli that can result in GBS, selective influenza vaccines and/or influenza viruses may contain cross-reactive antigens that stimulate the autoimmune response.

The majority of patients with GBS have had a recent infection due to respiratory viruses and/or gastrointestinal infections, especially *Campylobacter jejuni*. Cytomegalovirus infections have been implicated as another infection associated with an increased risk of GBS [210–212]. Influenza has been associated with GBS [210]. The preceding infections suggest a role for possible molecular mimicry in the pathogenesis of most GBS cases. The strongest evidence for molecular mimicry comes from GBS associated with *C. jejuni* infections where there is evidence that lipo-oligosaccharide moieties on the cell wall of the *Campylobacter* bacterium share antigenic and epitopic features to gangliosides expressed on human peripheral nerve, and induced antibodies against GM1 gangliosides result in neuronal damage [213,214].

5.7.1. Epidemiological evidence

The incidence of Guillain-Barré syndrome (GBS) is far too low to be picked up in clinical trials. Negative data from randomized clinical trials involving relatively small numbers of study participants does not rule out a causal association for uncommon or rare adverse events [215] and, with a background rate of about 1 case per 100,000 person-years, GBS cannot be evaluated in most clinical trials given their size.

A systematic review of the literature (see methods and appendix) identified 24 studies with unduplicated data that included a control group (including self-controlled studies) as described in Appendices 1 and 2. Of these 24 studies, 10 included the 2009–2010 influenza season. Study designs included cohort (9), case control (3), and self-controlled (12). Studies were conducted using US data (13), European (6), Canadian (2), Taiwanese (2) and an international collaboration including 10 other countries. Inactivated vaccines were the focus of 15 of these studies; however many of the publications did not specify which influenza vaccine(s) were studied. Only 4 of these studies included any meaningful data for children. Additional publications included subsets of the data published from the US studies in 1976–77 [216] and 2009–10 [217] and to reduce redundancy, these studies are not listed in Appendix 5. The epidemiological evidence assessing the relationship between GBS and influenza vaccines is based on these observational studies with a control group.

There are numerous case reports of GBS following influenza (and other) vaccines, two of which were reported prior to 1976. However, the 1976–77 swine flu vaccination program was the first time a vaccine was causally associated with GBS [216,218]. The emergence of a new strain of influenza in 1976 with similarities to the strain causing the 1918 flu pandemic led to the largest influenza vaccination program in the United States. While the feared pandemic never materialized, safety surveillance established for the vaccine program indicated two clusters of GBS in recent vaccinees reported in Minnesota and Alabama [216]. Surveillance for GBS was expanded to include the entire US, the vaccination program was halted, and careful epidemiological studies were conducted amid considerable public and political scrutiny.

With about 35 million vaccine doses administered, local and state health authorities contacted neurologists to ascertain cases of GBS. A standardized case reporting form was developed by the Centers for Disease Control and Prevention (CDC) to collect clinical and laboratory findings, antecedent events, medical histories, patient characteristics, and history of swine flu vaccination. Some states also surveyed non-neurologist practitioners and hospitals to identify additional cases. The incidence of GBS in vaccinated persons was compared to the incidence in unvaccinated persons.

Between October 1, 1976 and January 21, 1977, 1098 cases of GBS were identified [216]. Vaccinated persons were found to be 9.5 (95% CI: 8.2–10.3) times as likely to be identified as a GBS case compared to unvaccinated persons, translating into an estimated attributable risk of about 1 case per 100,000 vaccinees. The attack rate was lower in persons 18–24 years of age compared to older persons. The vaccine program was terminated before widespread vaccination of children was implemented and consequently there were not enough cases among children for meaningful study. The risk of GBS did not differ by type of vaccine, vaccine manufacturer, or vaccine lot suggesting the problem was not related to the manufacturing process. However, there were limitations to fully explore these issues. There was a clear temporal clustering of cases in the number of days after vaccination. The increase in risk was seen for

Guillain-Barre syndrome attack rates for population over 17 years of age, by week of onset after A/New Jersey influenza vaccination, United States, Oct 3, 1976-Jan. 29, 1977, excluding Arkansas, Connecticut, Delaware, and Washington. Data for California, Florida, Georgia, Missouri, North Carolina, New Jersey, New York, and Texas included for Oct. 3-Dec 18, 1976 only.

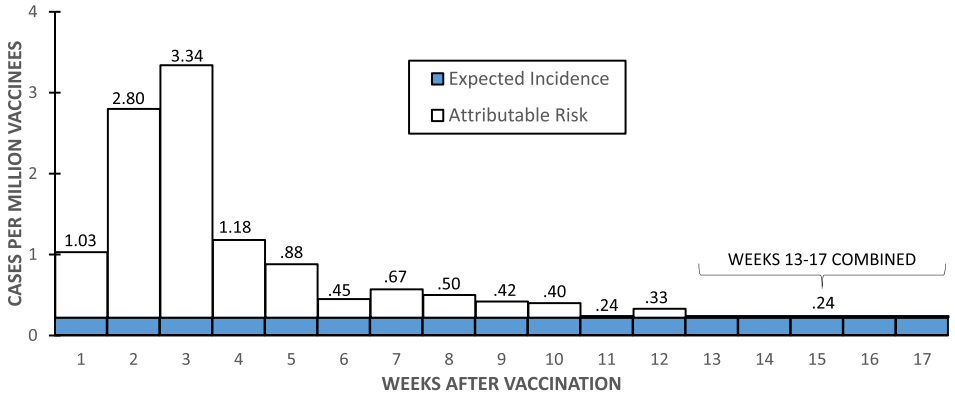

Fig. 4. Used by permission [216].

as long as 10 weeks after vaccination with the highest risk in the 2–3 weeks after vaccination and most of the risk occurred in the first 6 weeks post vaccination (see Fig. 4 from [216]). Rates of acute illnesses, a risk factor for GBS, were lower in vaccinated compared to unvaccinated cases, suggesting that the vaccine might have been serving as a trigger for some of these vaccinated cases who did not have another identified trigger. This risk was not seen among military personnel vaccinated in 1976–77 [220]. The US Institute of Medicine carefully reviewed these data and determined "the evidence favored acceptance of a causal relationship between the 1976–77 Swine Influenza vaccine and GBS in adults" [221]. While some controversy may always remain, the scientific community widely accepts that the 1976–77 influenza vaccine was an infrequent cause of GBS.

Enhanced surveillance has been undertaken since the swine flu vaccination program in 1976–77 to ensure that GBS was not a continuing problem with influenza vaccines. Eleven published studies have been conducted between the 1977–2008 influenza seasons. As can be seen in Appendix 5, most of these studies have been in the US (9 of 11) and did not find a statistically significant association between influenza vaccines and GBS. Two of these studies report a small, statistically significant increased risk for GBS associated with the vaccine ([222], relative risk 1.7; 95% CI: 1.0–2.8; [223], incidence rate ratio 1.45; 95% CI: 1.05–1.99). Together, these studies very convincingly demonstrate that the risk in 1976–77 has not occurred at nearly the rate in subsequent seasonal influenza vaccine formulations and, if influenza vaccines have been associated with GBS since 1976–77, the risk is extremely low. The US Institute of Medicine reviewed these studies from 1977 to 2008 and concluded that, aside from the 1976–77 vaccination program, the evidence was "inadequate to accept or reject a causal relationship between influenza vaccines and GBS."

One hypothesis to explain the much higher rate of GBS following the 1976 swine influenza vaccines was that the eggs used for production of the vaccines could have been contaminated with *C. jejuni* antigens [224]. However, careful PCR studies of residual vials of these vaccines found no evidence of *C. jejuni*. Immunization of mice with these vaccines did induce low levels of anti-ganglioside antibodies but influenza vaccines from other years also induced variable levels of anti-ganglioside antibodies in mice [224]. In other studies, rabbit polyclonal anti-ganglioside antibodies cross-reacted with several different H1N1 and H3N2 influenza viruses [225]. These investigators also studied mice injected with 1988–1989 and 2007–2008 or 2009 pandemic influenza vaccines and found minimal evidence for development of anti-ganglioside antibodies, which varied by mouse strain. The same investigators found no association between the antibody response in humans to influenza vaccines and the development of anti-ganglioside antibodies, but individuals over 60 were more likely than younger individuals to develop some anti-ganglioside antibodies. In another study, persons infected with the 2009 pandemic H1N1 influenza virus and individuals who were vaccinated with the 2009 pandemic vaccines did not develop anti-ganglioside antibodies [226]. The available evidence does not support the hypothesis that influenza vaccines induce anti-ganglioside antibodies that could be responsible for development of GBS, but additional studies are needed to investigate this and other possible mechanisms in genetically predisposed individuals [227,228]. Injection of myelin protein with adjuvants can induce neurologic syndromes in some animal species [229,230]. Therefore, studies were conducted to determine if there might have been inadvertent contamination of the 1976 vaccines with myelin protein. Studies of nine 1976 vaccines revealed no evidence of myelin P2 protein in the vaccines [229].

The 2009–10 influenza season afforded an opportunity to further examine the epidemiology of GBS. Concerns about a pending H1N1 pandemic led to mass immunization in many countries some of which had the capacity to conduct rigorous safety surveillance including, but not limited to, GBS. In the US, approximately 23 million vaccinated persons were under active surveillance for GBS through 6 large-linked databases capturing the general population as well as special populations. Extensive active surveillance for GBS post H1N1 vaccine was also conducted in many countries across Europe and Asia. Data were combined across Europe, in the US and in an international study including 10 countries (3 separate protocols). The US and international study benefited from a self-controlled case series (SCCS) methodology, comparing the risk of GBS in one time window to a second time window among vaccinated persons who contracted GBS. This approach has many advantages over comparisons between vaccinated and unvaccinated persons as these population groups may differ in important ways that would impact the incidence of GBS. While SCCS studies control for individual level variables (demographics, comorbidities, genetic variability) they are prone to bias if the disease of interest has seasonal or time dependent variability. H1N1 vaccines became available late in the 2009–10 influenza season when influenza circulation in many countries had already begun. Consequently, there was the potential for individuals to contract GBS after both receiving a vaccine and contracting influenza; studies may then be prone to inadvertently ascribe the vaccine, rather than natural disease, as the cause of GBS. Nonetheless, 2009–10

afforded an unprecedented opportunity to apply modern epidemiological tools to efficiently study extremely large and diverse populations.

A European case–control study recruited subjects from the UK, Denmark, the Netherlands, France and Sweden; 104 GBS patients were matched to one or more controls based on age, sex, index date and country [374]. The unadjusted pooled risk for all countries was 2.8 (95% CI: 1.3–60). However, the association between H1N1 vaccine and GBS no longer remained (adjusted odds ratio 1.0 (95% CI 0.3–2.7)) after adjusting for influenza-like illness/upper respiratory tract infection and seasonal influenza vaccine. The risk of GBS was higher but not significant (and unstable) among persons who received H1N1 vaccine and did not have influenza-like illness/upper respiratory tract infections. The study was prone to several biases, including the potential that people at increased risk of GBS might have been less likely to receive the vaccine and over-reporting or selective inclusion of exposed people with GBS.

Six active surveillance systems in the US conducted rapid assessment of the actual vs. expected number of cases (based on GBS incidence in previous years) and then conducted end-of-season analysis using self-controlled methods. Each of these systems showed a small increased risk (some reaching statistical significance) for GBS in the 42 days after vaccination compared to a comparison time window (days 50–91 post vaccination) [227,228,231–238]. A meta-analysis of these data found 54 cases in the vaccine exposure period compared to 23 cases in the control period ([217], incident rate ratio 2.35 (95% CI 1.53–3.68)). Fig. 5 [217] shows the preliminary results from the 6 active surveillance systems and the meta-analysis. Sensitivity analyses used different case definitions and stratified by receipt of seasonal influenza vaccine, more and less stringently defined influenza-like illness, time windows for vaccine exposure, and age. The results were remarkably consistent in these sensitivity analyses. Among people without influenza-like illness, the incident risk ratio for GBS in the 42 days post-H1N1 vaccination was 2.80 (95% CI 1.66–4.89). For people without influenza-like illness or fever or cough, the IRR was 3.00 (95% CI 1.72–5.47). These analyses suggest that wild influenza disease did not have an important impact on study findings. There did not seem to be a seasonality problem with the data as the incident rate ratios were similar between time periods. The risk did not vary by age; however the risk was not statistically significant among children (incident rate ratio 2.33 (95% CI: 0.65–10.46)) likely because of insufficient power in this subpopulation. With a consistent risk ratio across ages, the attributable risk ranged from 1 case per 1,000,000 vaccinations for persons <18 years of age to 3 cases per 1,000,000 vaccinations for persons 65 and older due to the increasing background rate of GBS by age.

An international collaboration including Australia, Canada, China, Denmark, Finland, the Netherlands, Singapore, Spain, the UK, the US (including some of the same US and UK cases) used two SCCS methods: (1) data were pooled across all sites; and (2) a meta-analytic approach which estimates rate ratios from each database were weighted based on within and between study errors and subsequently merged [239]. Sensitivity analyses were used to assess the effect of seasonal vaccine, different post-vaccination time windows, different case definitions, exclusion of missing data, and stratification by gender, age categories, history of GBS, presence of recent infections, and adjuvanted vs. non-adjuvanted vaccines. Seasonality was adjusted for in the meta-analytic approach. H1N1 vaccines were associated with GBS in the pooled analysis (relative incidence (RI) 2.86; 95% CI: 1.88–4.34)) and meta-analytic analysis (RI 2.42 (95% CI 1.58–3.72)). Sensitivity analyses found these results to be very robust. Excluding patients with reported influenza-like illness or upper respiratory illness in the 30 days before GBS onset slightly increased the risk estimate (RI 2.73; 95% CI 1.75–4.26) suggesting that the increased risk was not a result of circulating wild influenza virus. These finding are highly consistent with the US data. This study suggested a higher risk in adjuvanted vaccines (RI 2.97; 95% CI 1.13–7.84) than non-adjuvanted vaccines (RI 1.88; 95% CI 1.03–3.41); however the difference was not statistically significant. Age-stratified analysis suggested a trend rather than statistically significant differences in relative incidence by age. Among children (<19 years), the RI was 0.73 (95% CI 0.16–3.46).

Many of the country and surveillance specific data that make up the European, US and international study are also published independently. The combined data are described as they offer the most power and benefit from a standardized protocol. Two additional studies of GBS in 2009–10 that were not a part of these coordinated efforts are published separately and shown in the table in Table 5, lines 17 and 18. A SCCS of 2009–10 H1N1 vaccine in Germany found an increased relative incidence of GBS (4.65 (95% CI 2.17–9.98)) [240]. A SCCS of 2009–10 H1N1 vaccine in Taiwan found an IRR of 3.81 (95% CI 0.43–33.85) [241].

Several epidemiological studies including influenza seasons after 2009–10 [242–244] revealed non-significant point estimates of an increased risk of GBS following influenza vaccine and the confidence intervals are consistent with the findings from 2009 to 10; however these studies are under-powered to definitively identify such a small increase in risk. One study after 2009–10 [152] found a decreased risk of GBS (relative risk 0.5; 95% CI 0.3–0.9), perhaps

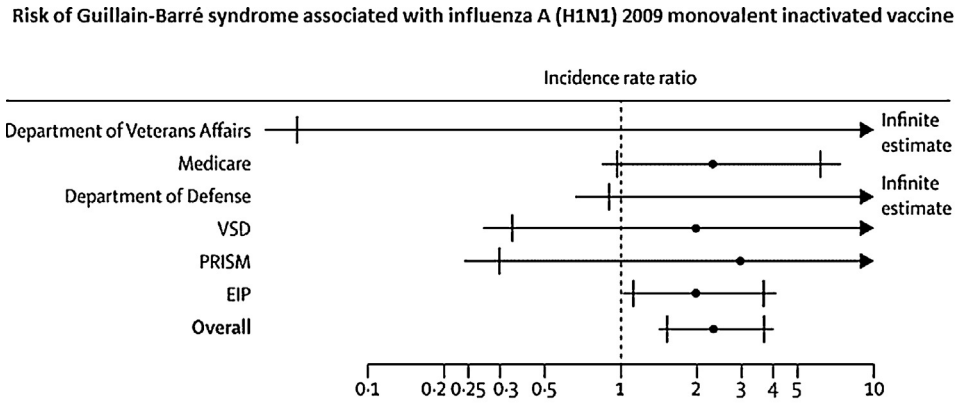

Fig. 5. Used by permission [217].

explained by problems with the comparator group some of whom may have been vaccinated with the 2009–10 H1N1 vaccine which has been shown to be associated with GBS.

While there are 22 epidemiological studies since 1976–77 examining the relationship between influenza vaccines and GBS (Appendix 5, lines 3–24), there is not a clear consensus in the scientific community regarding the interpretation of these data. The 2009–10 U.S meta-analysis and the international collaborative study from the same year are likely the strongest methodologically. These findings of a roughly doubling of risk of GBS in the 42 days after influenza vaccine are consistent with nearly all the studies done since 1976–77; the majority (18 of 22) of these studies' confidence intervals overlap with 2.0. Doubling the risk of GBS during a 42-day risk window translates into 1–3 excess GBS cases per million persons vaccinated. The benefits of influenza vaccine, including prevention of GBS caused by influenza, greatly outweigh this very small risk. When studied with adequate power, differences in risk have not been observed between types of influenza vaccines; however some vaccines such as live attenuated and adjuvanted vaccines have not been studied as extensively as the non-adjuvanted inactivated vaccines (Appendix 5). Only two of these studies have been conducted outside the US, Canada and Europe. Consequently, it is problematic to generalize these data to countries where there may be differences in genetics and in the health status of the population (nutrition, concurrent and past infections). The vast majority of these data are among adults, primarily because influenza vaccine recommendations for children are relatively new in many countries. Only 3 of 24 studies provide data on children and these findings are inconclusive (Appendix 5).

5.7.2. Conclusions

Epidemiological studies provide convincing evidence that the 1976–77 vaccine caused GBS among adults. Since 1976–77, the epidemiological evidence indicates a small increased risk of GBS among adults of approximately 1–3 per million doses of IIV. Inconsistent findings in several studies can largely be explained by lack of statistical power among negative findings. The biological mechanism(s) for the small increased risk following inactivated influenza vaccines is not understood. The small increased risk associated with IIV appears to be much lower than the risk associated with influenza infections [210]. Epidemiological evidence is insufficient in children and for live attenuated vaccines to draw any conclusions.

5.8. ADEM

Acute disseminated encephalomyelitis (ADEM), Multiple sclerosis (MS), and transverse myelitis (TM) are demyelinating disorders affecting different areas of the central nervous system. These diseases have several characteristics in common, including inflammatory pathological focal lesions in the central nervous system that are often preceded by infections, especially influenza [223,224,241,242]. The pathogenesis is not fully understood for any of the diseases but appears to involve genetic predisposition and autoimmune responses triggered by acute infections [227,228,245,247]. The animal models for experimental autoimmune encephalomyelitis (EAE) are a possible model for what occurs with MS and/or ADEM [388]. However, these animal models involve injection of myelin and/or other CNS tissues with complete Freund's adjuvant. There is no myelin or other CNS tissue present in influenza vaccines and there is no animal model that reproduces the observations of CNS demyelinating diseases in humans following natural infections or vaccines.

The focal inflammatory lesions in ADEM affect primarily white matter in the brain and spinal cord [247]. There are no specific laboratory tests for making the diagnosis of ADEM; the diagnosis is based on clinical criteria and the results of CNS imaging [227,228,247,248]. Inconsistencies in criteria for defining ADEM have resulted in variability in the clinical illnesses reported in association with infections and/or vaccines. Illnesses that might have been ADEM have been called by other names such as "brain stem encephalitis" or "post-vaccination encephalitis" prior to the availability of MRI and CT scans and standard definitions. Some published case-reports of ADEM following influenza vaccines would not meet criteria most neurologists accept today. In some reports, neurologists have not attempted to differentiate ADEM from other disorders including encephalitis. ADEM has been reported in all age groups with a predominance of cases in males and children [248,249].

5.8.1. Case definition

ADEM is a usually defined as a monophasic illness associated with brain inflammation and demyelination involving primarily white matter [227,228,250]. ADEM definitions have varied. Some authors have noted that ADEM can be diagnosed without a preceding infection or vaccine. Authors often include evidence of a recent infection or receipt of a vaccine as a criteria for the diagnosis [250,389]. In 2007, the Brighton Collaboration established a standardized definition for ADEM [247]. The Brighton Collaboration recognized that an infection or vaccine may or may not have been a causal or contributing factor in the development of the disease. Also, the definition should not include a prespecified time interval for a possible causal factor to have occurred prior to the onset of disease as doing so again suggests a causal or contributing factor in the development of the disease.

The Brighton collaboration criteria require that ADEM is a monophasic illness. Patients that relapse after a 3-month interval have other diseases, most commonly MS [251,247]. Although these criteria have resolved inconsistencies in previous definitions of ADEM, not all groups have followed the lead of the Brighton Collaboration and continue to use other less rigorous case definitions. The Pediatric Multiple Sclerosis Study Group has continued to use criteria for ADEM that include a preceding infection or vaccine [389]. In 2012, this group proposed a revision to their case definition for ADEM in order to assist with the differentiation between ADEM and MS because they note that ADEM recurrences are noted in 2–18% of cases and some patients with recurrences do not meet the criteria for MS [389].

5.8.2. Causality assessment

Biologic plausibility for influenza vaccines to be a possible trigger for ADEM comes from the observation that up to 90% of patients with ADEM have a preceding infection or have received a vaccine [247]. Respiratory infections, including influenza-like illnesses, have been frequently documented prior to the onset of ADEM and influenza virus has been identified in nasal secretions at the time of onset of neurological symptoms in several patients with ADEM [227,228,247,252,390]. ADEM has been reported after several different vaccines, including inactivated and live attenuated influenza vaccines in the United States [247]. A recent review identified 71 published reports of ADEM following vaccines including 21 reports following influenza vaccines published from 1979 to 2013 [391]. Most reviews of ADEM published in respected peer-reviewed journals and chapters in textbooks of neurology conclude that immunizations, including influenza vaccines, are a contributing or causal factor [249,248,251]. The bases for this conclusion are temporal associations, biologic plausibility, and possibly extensions of logic from experience with the Semple rabies vaccine which contained myelin basic protein and caused neurologic illnesses [227,228,253]. The Semple vaccine is the only vaccine with evidence of a causal relationship with ADEM or an ADEM-like illness; the peak onset was one to two weeks after vaccination [247].

Smallpox vaccines were associated with neurologic disorders labeled encephalitis, but the illnesses were consistent with ADEM, although imaging studies were not available for most affected individuals diagnosed at that time [227,228,254]. In some reports, the assumption of a causal association was, "Based on the temporal association and exclusion of alternative etiologies" [255]. However, it is impossible to rule out all alternative causes because ADEM has been reported following a many viral and bacterial illnesses and no one knows the entire list of infectious diseases that might trigger the development of ADEM [256,257].

5.8.3. Mechanistic evidence

No biologic evidence directly implicating influenza or other vaccines in the pathogenesis of ADEM has been identified. In the future, investigators might be able to identify specific immunologic markers responsible for the demyelinating inflammatory processes that will help confirm or rule out a vaccine in the pathogenesis of ADEM.

5.8.4. Epidemiologic evidence

There are limited epidemiologic studies evaluating a possible causal relationship between influenza vaccines and ADEM. Using population-based data in Sweden, investigators conducted a retrospective cohort study for selected outcomes in a population of 5,845,039 individuals (61% of the Swedish population) where 57% of the population received the AS03 adjuvanted 2009 H1N1 vaccine [258]. Investigators identified an increased risk of narcolepsy associated with the vaccine (see narcolepsy section below) but there was no significant increased risk of ADEM or other neurologic events associated with the vaccine. The hazard ratio was 1.41 (95% CI 0.35–5.73) based on three cases of ADEM in the 6 weeks following the vaccine [258].

The rates of reported neurologic events, including ADEM, following pandemic H1N1 influenza vaccines did not differ for adjuvanted vs. unadjuvanted vaccines in the EudraVigilance surveillance system, but these data cannot be used to determine causal associations as no control populations were studied [259]. One child with ADEM after an AS03 adjuvanted pandemic H1N1 influenza vaccine was reported in Canada [260].

5.8.5. Other reviews

The Clinical Immunization Safety Assessment (CISA) network estimated the biologically plausible time window for ADEM following immunizations should be from 48 h to six weeks [26,27]. Case reports of ADEM with onset less than 48 h following influenza vaccines have concluded the vaccine as a causal factor, even though it appears to be too short an interval for an immune response with an inactivated vaccine to cause this type of illness [26,27,261]. CISA reviewed individual cases of ADEM following vaccines and concluded that the causal evidence was indeterminate based on the causality algorithm [62,262,263]. In 2011, the IOM concluded that the evidence was "inadequate to accept or reject a causal relationship between influenza vaccine and ADEM" ([7] p. 309). Similar conclusions were reached by other experts following a detailed review of the evidence regarding vaccines causing neurological events. CDC investigators commented that "although specific incidents cannot be excluded, and the current available evidence cannot determine that particular host factors in predisposed individuals may in some cases result in neurologic disease following a particular vaccine, the overwhelming evidence suggests that currently utilized vaccines are safe and not associated with increased risk of neurologic illness" [227,228].

In summary, the available evidence does not establish a causal relationship between influenza vaccines and ADEM, but the evidence cannot rule out the possibility of a small increased risk. There is no evidence to suggest that any one type of influenza vaccine may be more or less likely to be associated with ADEM.

5.9. Multiple sclerosis

Multiple Sclerosis (MS) is an autoimmune chronic inflammatory disease affecting various areas of the central nervous system associated with demyelination and axonal loss [264]. Case definitions for MS have evolved over the past 15 years and different criteria are used for establishing the diagnosis in pediatric patients [264].

As with other autoimmune diseases, there is evidence for a genetic predisposition. Multiple genes have been associated with MS and there is evidence for different rates of disease in different ethnic groups [264]. The pathogenesis appears to involve T cells, B cells, antibodies, and most likely the innate immune system. Environmental factors believed to contribute to the pathogenesis include decreased exposure to sunlight, vitamin D deficiency, infections, and passive exposure to cigarette smoke [264]. Multiple infectious agents have been investigated as possible contributing factors without clear and convincing evidence for any single infectious agent. The focus of attention in recent years has been on Epstein–Barr virus (EBV), herpes simplex virus type I (HSV-1), and cytomegalovirus (CMV) infections early in life. The evidence for an association with EBV infection has biologic plausibility because the primary genetic marker associated with MS (human leukocyte antigen (HLA)-DRB1) codes for a co-receptor for EBV entry into cells [264,265]. Some studies found an increased prevalence of antibody to EBV in children with MS [265]. However, a recent study of 189 children with MS found no differences in antibody to EBV, HSV-1, or CMV [393]. Associations between HSV-1 had either a protective effect or increased risk depending on other genetic markers in patients with MS; some data suggested that CMV infections could be a possible protective factor [392].

MS must be differentiated from several other neurologic disorders. Many patients have an initial episode of neurologic illness diagnosed as ADEM that later is found to be MS based on relapses and additional clinical criteria. Most affected individuals have onset as adults, but 1.7–5.6% in different populations have onset prior to 18 years of age [264]. The majority of pediatric cases have onset at 13–16 years of age, but cases have occurred in individuals less than 10 years of age. The incidence is higher in temperate climates than tropical climates and risk may be related to decreased exposure to ultraviolet light.

Authors of case reports have made the assumption that since infections play a role in the pathogenesis of MS, vaccines, including influenza vaccines, could cause or exacerbate MS.

5.9.1. Epidemiological evidence

The incidence of MS is too low to be detected in clinical trials. Finding no increased risk in randomized clinical trials involving relatively small numbers of study participants with limited follow-up does not rule out a causal association for uncommon or rare adverse events [215]. With an annual incidence of about 0.5 cases per 100,000 person years among children [264], MS risk cannot be evaluated in moderate sized clinical trials.

A systematic review of the literature (see Methods and Appendices 1 and 2) identified 7 studies (with some duplication of data among two of these studies) that included a control group (Appendix 6). Four of the 7 studies were case–control studies and 3 were cohort studies. Inactivated vaccines were the focus of 6 of these studies. Only 2 of these studies included meaningful numbers of children and results were not stratified by age. Four of these studies were conducted in Europe and one each in Canada, the US, and Taiwan. All 7 studies found no relationship between MS onset with influenza vaccination.

The IOM reviewed data through the 2008–09 influenza season and concluded that there was limited epidemiological evidence regarding influenza vaccines and MS onset among adults [7]. The IOM based their conclusions on two of the studies in Appendix 6

([266,267], lines 2–3) and did not consider one of the studies in Appendix 6 ([268], line 4) because of serious methodological limitations. One additional study ([269], Appendix 6 line 2) was not identified by the IOM and is described below. Subsequent to the IOM review three additional studies have been published examining MS onset and influenza vaccines, described below.

A case–control study was conducted in Italy among 140 consecutive patients at an MS center who were matched by age and gender with 131 blood donor controls ([269], Appendix 6 line 2). Results of this study indicated that influenza vaccines were not associated with MS (OR 1.6, 95% CI 0.7–3.3).

A retrospective cohort study was conducted of all residents of Stockholm, Sweden in the 2009–10 influenza vaccination season ([197], Appendix 6, line 4). The study included nearly 2 million people, 52% of which were vaccinated with 2009–10 pandemic A/H1N1 (some with AS03 adjuvant). MS and other outcomes were identified by International Classification of Diseases, 10th revision (ICD-10) codes for hospital admissions and visits to specialty care. The study found 3795 MS cases among vaccinated and unvaccinated persons, with an adjusted odds ratio of 0.93 (95% CI 0.68–1.26). Children were included in the study but results were not stratified by age. The study did not consider prior influenza vaccination nor were ICD-10 diagnostic codes validated with chart review.

A prospective cohort study ([258], Appendix 6, line 6; note some overlap with [197], Appendix 6, line 4) monitored disease in all 7 Swedish regions associated with the immunization campaign against the 2009 influenza pandemic. With nearly 6 million residents, about 57% received 2009–10 pandemic A/H1N1 (some with AS03 adjuvant), with higher vaccination rates among children. ICD-10 codes were identified from hospitalizations and non-primary care outpatient visits, identifying 1003 incident MS cases, for an adjusted odds ratio of 1.04 (95% CI 0.95–1.15) for vaccinated compared to unvaccinated individuals. Children were included in the study but results are not presented stratified by age. The study did not consider prior influenza vaccination nor were ICD-10 diagnostic codes validated with chart review.

The third study published since the IOM review ([270], Appendix 6, line 5) was a small retrospective study conducted in Taiwan with 8 cases aged 65 years and older, finding an adjusted odds ratio of 0.35 (95% CI 0.07–1.77) for vaccinated compared to unvaccinated persons.

A meta-analysis [271] combined data across the four studies in Appendix 6 published before 2011 ([266], line 1; [269], line 2; [267], line 3; and [268], line 4) and found no relationship between influenza vaccines and MS (odds ratio 0.97, 95% CI 0.77–1.23).

Six studies that included a control group examined associations between influenza vaccines and MS relapse; 4 were clinical trials, 1 was a case-crossover, and 1 was a cohort study. Inactivated vaccines were the focus of 3 of these studies. Four of these studies were conducted in the US, 1 in Israel and one in Europe. All six studies found no relationship between MS relapse associated with influenza vaccination.

The IOM concluded that there was limited confidence in the epidemiological evidence regarding influenza vaccines and MS relapse, considering data through the 2008–09 influenza season. The IOM based their conclusions on the two studies in Appendix 6 ([272], line 9 and [273], line 11). The IOM determined one of the studies included in Appendix 6 ([274], line 10) was too small to be informative and the publication did not state if the treatment assignment was random. The IOM review did not identify two of the studies included in Appendix 6 ([275], line 7; [276]) and did not include one study in Appendix 6 ([277], line 12) as it was published beyond the time frame of the IOM review. These two studies in Appendix 6 not considered by the IOM ([275] line 7; [276], line 8; [277], line 12) were all relatively small (122 cases among the 3 studies).

A meta-analysis [271] combined data across four studies in Appendix 6 published before 2011 ([275], line 8; [276], line 9; [272], line 10; and [274], line 11 ([273], line 12 was not included in this meta-analysis)) finding no relationship between influenza vaccines and MS relapse (odds ratio 1.24, 95% CI 0.89–1.72).

Two letters to the editor were published with data on MS relapse that are not included in our table as they are not research articles identified by the systematic search (see appendix for methods). In a self-controlled case series, 137 MS patients with definitive clinical diagnosis of relapsing-remitting MS in Argentina were offered monovalent H1N1 and trivalent seasonal vaccine containing the H1N1 strain [394]. Risk windows of 30, 60 and 90 day risk windows following vaccination were evaluated and compared to control windows of up to 11 months following vaccination. The relapse ratio for risk vs. control window was 0.86 (95% CI 0.2–3.6) for the 30-day risk window and similar results were found in the secondary analysis for 60- and 90-day risk windows. A case-crossover study conducted among MS patients who attended an acute relapse clinic in the UK in 2009–10 suggested the possibility of an increased relapse rate associated with H1N1 influenza vaccine [278]. Among 30 consecutive patients with relapses, 10 patients (33.3%) had received H1N1 vaccination within 3 weeks prior to relapse compared to lower rates in the control periods prior to relapse (relative risk 6.0, 95% CI 1.4–26.2). The authors acknowledge several limitations, including small numbers of patients studied, but this report has other limitations, including selection of patients during the time when H1N1 vaccine was administered and picking a shorter risk window than other investigators have used. Also, information was not provided to document lack of referral bias to a clinic with an interest in influenza vaccine as a possible trigger for MS relapses.

5.9.2. Summary and conclusions

The hypothesis that influenza vaccines could cause MS onset or relapse was based on the belief that infectious agents may trigger MS in genetically susceptible populations and case reports showing a temporal relationship between receipt of influenza vaccines and onset or relapse of MS. Epidemiological evidence indicates that exposure to environmental factors in the first 15 years of life is associated with the risk of development of MS. In recent years, investigators have focused on EBV, HSV-1, and CMV as possible factors associated with MS as there is some biologic plausibility for these viruses to have an interaction with the underlying genetic factors that have been identified. There is much less interest in influenza infection or vaccines as causative factors because of consistent negative findings with regard to association with risk of MS in multiple studies and no biologically plausible mechanism has been identified to explain how these exposures early in life contribute to the risk of MS later in life. Although each of the epidemiological studies reported to date has had relatively low power to rule out an increased risk, these studies as a group provide consistent evidence against a causal association between influenza vaccines and MS onset or relapse among adults. Studies are more limited in children due, in part, to the lower risk of disease but there is no signal to indicate evidence of concern. Taking all of the evidence into consideration, it is highly unlikely that the influenza vaccines studied to date are associated with MS onset or relapse among children or adults.

5.10. Narcolepsy

5.10.1. Background

Narcolepsy is a chronic disorder of excessive daytime sleepiness associated with loss of hypocretin secreting cells in the hypothalamus and absence of hypocretin in the cerebrospinal fluid [279]. Many affected individuals also have cataplexy, sudden episodes of voluntary muscle weakness, including collapse. The diagnosis of narcolepsy based on the International Classification of Sleep

Disorders requires the presence of excessive daytime sleepiness and cataplexy or abnormally low CSF hypocretin-1 concentration, with some modifications for young children [279]. The Brighton collaboration level I criteria include excessive daytime sleepiness or cataplexy, and CSF hypocretin-1 deficiency [280]. Criteria for level 2 or level 3 do not require measurement of CSF hypocretin-1, but do have requirements for abnormal test results based on the Multiple Sleep Latency Test (MSLT). All levels require the absence of other mimicking disorders.

The onset of narcolepsy is usually after four years of age, with a peak onset between 10 and 30 years of age [279]. Prior to the publicity about narcolepsy in 2010, the diagnosis was often delayed for several years after onset of symptoms due to the nonspecific nature of presenting signs and symptoms, and the need for definitive tests at referral centers. There is evidence for a genetic predisposition to narcolepsy. Almost all affected pediatric patients have the HLA-subtype DQB1*602, but only a small proportion of individuals with this marker developed narcolepsy. Environmental factors, including infections, appear to play a role in triggering the onset of disease. These observations have led to the hypothesis that narcolepsy is an autoimmune disease [279,281]. Several candidate mechanisms for autoimmunity have been proposed with inconsistent findings [279,281,282]. One study found evidence for cross reactivity between an influenza virus nucleoprotein and a hypocretin receptor and that patients with vaccine-associated narcolepsy had antibodies to this receptor [409]. Several studies have revealed that patients with narcolepsy are more likely to have antibodies to *Streptococcus pyogenes*, commonly known as group A beta-hemolytic streptococcus, a common cause of pharyngitis and skin infections, or higher titers of antibodies to streptococcal antigens as summarized in a recent review [279].

The prevalence of narcolepsy varies by ethnic group and geographic region from 0.23 per 100,000 people in Israel to 160 per 100,000 people in Japan, with an overall geometric mean of approximately 30 per 100,000 people [279]. This variability in background rates of narcolepsy generally corresponds to different prevalence rates of the HLA-subtype DQB1*602 markers in Europe and North America (see Fig. 6) [279]. However, there are no data on the prevalence of narcolepsy in areas of Africa where there is a high prevalence of the HLA-subtype DQB1*602.

Eight different pandemic H1N1 influenza vaccines were licensed and used in Europe in 2009–2010. Approximately 39 million doses of a pandemic H1N1 vaccine produced by GlaxoSmithKline (Pandemrix) containing AS03 adjuvant were administered in Europe [283]. Smaller numbers of the other vaccines were administered to selective populations in some countries. Active monitoring of reports of adverse events in most countries during the large-scale campaigns to administer pandemic 2009 H1N1 vaccines did not detect unusual numbers of reports of narcolepsy following the vaccines in most countries [284]. In Finland and Sweden, dramatic increases in the rate of diagnoses of narcolepsy were noted in children following the immunization campaigns. The majority of children who developed narcolepsy had received pandemic H1N1 vaccine [285,375]. These concerns were initially met with skepticism, but population-based epidemiologic studies confirmed an increased risk associated with the vaccine [258,283,286,395].

In Finland, a retrospective cohort study was conducted among 4–19 year-old children [286]. Cases meeting levels 1–3 of the Brighton collaboration criteria were included and, in the primary analysis, only cases diagnosed prior to publicity about a possible causal relationship with the vaccine were included. There are often long delays from the onset of symptoms to establishment of a diagnosis at a referral center. The primary analysis used time to first contact with a healthcare provider for the onset of disease. The incidence of narcolepsy among vaccinated children was 9.0 per 100,000 person years compared to 0.7 per 100,000 person years for unvaccinated children for a rate ratio of 12.7 (95% CI 6.1–30.8). Sensitivity analyses revealed statistically significant elevated rate ratios using (a) different time periods for inclusion of cases to evaluate the impact of publicity on case recognition, (b) time from vaccination to parental recall of symptom onset, (c) time to referral to a specialist, and (d) time to diagnosis (see Fig. 7).

Retrospective cohort, case–control, self-controlled case series, case coverage, and self-controlled risk interval studies were conducted in other countries. These studies used different time windows for comparison of incidence rates before and after vaccination, comparisons between vaccinated and unvaccinated populations, the dates used for capture of cases, and the statistical tests applied. Studies in Sweden, Norway, Ireland, England, and France revealed significant increases in risk associated with the vaccine (Appendix 7). The estimated relative risks (RR), odds ratios (OR), or incidence rate ratios (IRR) ranged from 2 to 16.

The increased risk was primarily in children, but studies have revealed smaller elevated risks in adults in France, Sweden, and

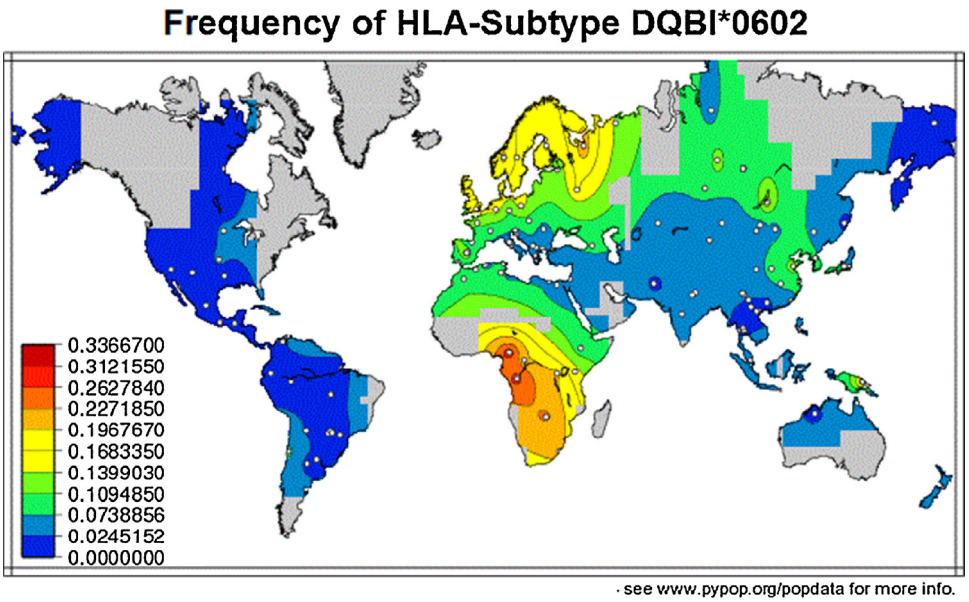

Fig. 6. Used by permission [378].

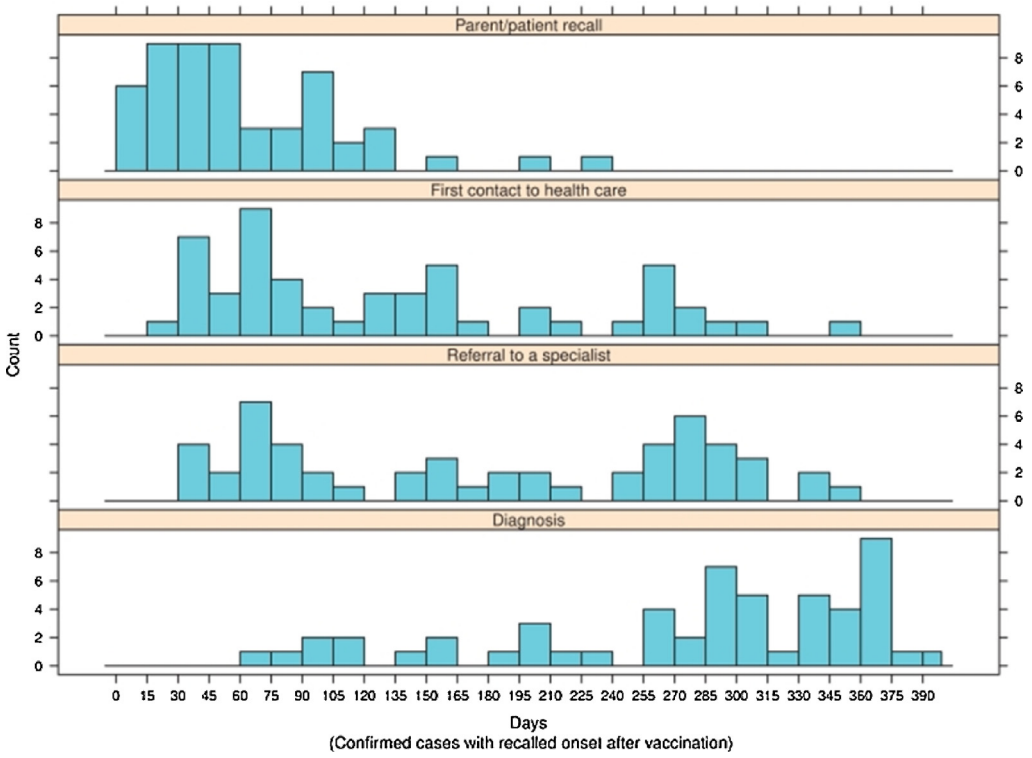

Fig. 7. Used by permission [286].

Finland. In France, a case–control study of patients with narcolepsy with cataplexy from 13 centers matched with multiple controls, found an odds ratio of 6.5 (95% CI 2.1–19.9) in subjects <18 years of age, and 4.7 (95% CI 1.6–13.9) for those 18 and over [396]. In Sweden, a 2-fold increase in risk was noted in individuals 21–30 years of age [279]. In Finland, a 3–5 fold increased risk was noted in adults 20–64 years of age with an attributable risk of 1/100,000 person years as compared to 6/100,000 person years for children [287].

Upon a request from the European Medicines Agency (EMA), The ECDC (E219) and the Vaccine Adverse Events Surveillance and Communication consortium (VAESCO) coordinated a case–control study in both children and adults in Denmark, Finland, Italy, the Netherlands, Norway, Sweden, and the UK (E219). Cases met Brighton Collaboration criteria. The same cases included in the study were also included in the individual country studies. Controls were selected from the same population and matched on age, sex, and index date. In the primary analysis the timing for cases was based on the referral to the MSLT; in the sensitivity analysis to use time to onset of excessive daytime sleepiness and time to diagnosis. In the signaling countries of Sweden and Finland, a highly significant association was found with exposure to the AS03 adjuvanted vaccine (OR 14.2 (95% CI 2.5–infinity) for children and adolescents. No significant association was found in adults (OR 1.2 (95% CI 0.2–9.1). In the non-signaling countries, no significant associations with the vaccine were found for children and adolescents 1.6 (95% CI 0.5–6.1), or for adults (OR = 3.7 95% CI 0.7–20.7) (E219).

VAESCO also compared the rates of narcolepsy diagnoses in the nine years prior to the immunization campaign and the year following the campaign in large linked databases for health outcomes in Sweden, Finland, the UK, the Netherlands, Denmark, and Italy [289]. This study confirmed increases in rates of diagnosis of narcolepsy in Sweden, Finland, and Denmark following immunization campaign, but did not identify increases in the other countries. In Denmark, which used a different vaccine, the cases included were not confirmed and some had onset prior to vaccination. A follow-up report from the Netherlands Pharmacovigilance Center indicates that there may have been a number of cases that had not been diagnosed at the time of the VAESCO report, and that many of these were in children under five years of age. Many of the cases included in the above two studies have been included in reports from the individual countries; these are not independent studies.

An AS03 adjuvanted pandemic 2009 H1N1 vaccine (Arepanrix®, GlaxoSmithKline Inc.) used in Canada was manufactured at a different location than the vaccine used in Europe with some differences in production methods [281,283]. No signal of an association between this vaccine and narcolepsy was noted during the active monitoring period. In Ontario, Canada, 4.8 million doses of Arepanrix® were administered in a population of 13.2 million. Among the 1603 reports of adverse events following immunization in 2009 and 2010, no cases of narcolepsy were identified among persons 4–29 years of age [2]. In Québec, analyses were conducted using cases meeting Brighton Collaboration criteria and analyzed by three different methods [377]. A retrospective cohort study revealed a RR of 4.58 (95% CI: 1.59–11.77) based on a small number of cases (see Appendix 7). The absolute attributable risk estimate was about 1 case per million vaccine doses. A self-controlled case series analysis revealed a RR of 4.82 (95% CI: 1.75–13.31). For persons <20 years of age the RR was 6.39 (95% CI 1.6–23.38) and was not significantly increased for those ≥21 years of age. A case–control study using the same patients revealed a non-significant OR of 1.48 (95% CI: 0.37–7.03). The OR was 3.21 (95% CI: 0.37–90.37) among persons less than 20 years of age (6 exposed vs. 2 not exposed) and was 0.73 (95% CI: 0.06–6.70) among adults (2 exposed vs. 3 not exposed).

Differences in the risk estimates for associations between the Pandemrix vaccine in different countries may be due, in part, to differences in the prevalence of the HLA-subtype DQB1*602 [279]. The strongest associations were in northern Europe with intermediate rates in the rest of Europe and a lower risk in Canada, consistent with the relative frequencies of the prevalence of HLA-subtype DQB1*602 markers.

No cases of narcolepsy have been reported as adverse events following the distribution of 23.26 million doses of a pandemic 2009 H1N1 influenza vaccine containing the MF59 adjuvant in Europe [281,290]. No studies have been published with the other 6 vaccines used in Europe indicating any evidence of an increase in risk of narcolepsy following these vaccines. In a claims-based system in the United States involving 12 million persons (approximately 4% of the US population), no increased risk of narcolepsy was detected in the 90 days following vaccination using electronic medical records and the self-controlled risk interval method for the monovalent vaccine used in 2009, or trivalent seasonal vaccines used in 2009–10 or in 2010–11 [291]. Also, no cases were noted in the 180 days following administration of 650,995 doses of the 2009 pandemic 2009 H1N1 influenza vaccine without an adjuvant in the VSD population. In the following year, only 2 cases were noted in the 180 days following administration of the seasonal vaccine when 8.83 cases would be expected based upon the baseline incidence rate in the US population [292].

Historically, clinical descriptions of a disorder called "encephalitis lethargica", which could have been narcolepsy, were reported following the 1918 H1N1 influenza pandemic [397]. There is evidence for seasonality in the reported diagnoses of narcolepsy consistent with influenza infections as a trigger factor, and an increase in diagnoses of narcolepsy was temporally associated with H1N1 disease at one sleep disorder center in China where no H1N1 vaccines were administered, with a subsequent decline in reported cases the following year [293]. However, no increase in narcolepsy diagnoses associated with the pandemic virus has been reported from other countries affected by this pandemic virus where the AS03 adjuvanted vaccine was not used, including the United States and South Korea [279]. There was also speculation that infection with the H1N1 virus along with exposure to the AS03-adjuvanted vaccines could have resulted in an increased risk of narcolepsy. However, in Finland less than 10% of the children who developed narcolepsy had a history of a respiratory infection prior to the onset of illness [279]. Also, only 2 of 45 children in Finland who developed narcolepsy had evidence of antibody to a nonstructural protein in the H1N1 virus that was not present in the vaccine [294].

Speculation that a unique viral protein in combination with the AS03 adjuvant could have explained the higher risk associated with the Pandemrix vaccine than the vaccine used in Canada [281]. The final data from Québec revealed some increased risk associated with the Arepanrix vaccine [377]. The estimated attributable risk in Canada was one per million children immunized, as compared with one per 16,000 in Finland. This difference in risk could be due to differences in manufacturing processes and/or the prevalence of genetic predisposition to narcolepsy [283]. Pandemrix vaccine contained higher amounts of a structurally altered viral nucleoprotein than Arepanrix, and children with narcolepsy had higher antibody responses to this protein than did control children. These differences in vaccine composition might explain the differences in the risk of narcolepsy [295,409].

One report of CD4+ cells in persons with narcolepsy cross-reacting with hypocretin was subsequently withdrawn because of an inability to reproduce the results [296].

5.10.2. Summary and conclusion

The evidence from multiple studies by different investigators in different populations using different methods has revealed a consistent strong association between the Pandemrix vaccine receipt and narcolepsy. The geographic differences in estimated risks are consistent with the geographic distribution of genetic markers associated with narcolepsy. This evidence indicates a causal relationship with narcolepsy. The evidence available to date does not indicate any increased risk of narcolepsy associated with other influenza vaccines, including vaccines without an adjuvant and the MF59-adjuvanted vaccine. Further studies are needed to identify the biological mechanisms responsible for increased risk of narcolepsy.

5.11. Bell's palsy

5.11.1. Definition

Bell's palsy (seventh cranial nerve paralysis) is an acute unilateral lower motor neuron facial paralysis. The definition of Bell's palsy has evolved and varied over time [297]. The Brighton Collaboration has a working group developing a standard definition of Bell's palsy. Key features generally include: acute onset, peripheral nerve involvement, unilateral, non-recurrent, complete, monosymptomatic, and idiopathic. This monosymptomatic illness can manifest with varying severity: ranging from mild paresis to complete paralysis. Reactivation of HSV-1 or varicella zoster virus and Lyme disease are recognized predisposing infections to paralysis of the seventh cranial nerve [297]. Some authors consider these infections to be diagnoses of exclusion for Bell's palsy and others list them as known causes of the conditions. The incidence of Bell's palsy in adults is 25 per 100,000/year [298]. The annual incidence of Bell's palsy is 2.7 per 100,000 children under 10; the rate incidence increases to 10.1/100,000 for persons 10–20 years of age [297].

The pathophysiology of Bell's palsy is not completely understood. In children, the onset usually occurs hours to days after an upper respiratory tract infection and resolves spontaneously without treatment. In some cases, it is inflammation of the facial nerve with mononuclear cells [298] and this can be due to infection or an inflammatory process. The inflammation of the facial nerve and entrapment in the meatal foramen and the labyrinthine segment [297] lead to the disorder. The pathogenesis in some instances may be due to a post-infectious demyelinating process [297]. Bell's palsy may be preceded by sensory disturbances, pain behind the ear, loss of taste unilaterally on the tongue [297,298]. Infections most commonly associated with Bell's palsy include Lyme disease, HSV-1; varicella zoster virus reactivation in the geniculate ganglion with or without vesicular rash (Ramsay Hunt syndrome), with other viruses causing it less commonly.

5.11.2. Causal association

There is no known association between influenza virus infection and Bell's palsy [246,299]. Bell's palsy associated with influenza vaccine was first reported after the introduction of an inactivated virosomal-subunit intranasal influenza vaccine that was adjuvanted with *E. coli* heat-labile (LT) toxin. This vaccine (Nasalflu®) was developed by Berna Biotech and licensed in Switzerland for the 2000–2001 influenza season. The vaccine was first available in October 2000 and by April 2001, 46 cases of Bell's palsy after vaccination had been reported [300,399]. A total of 412 patients with Bell's palsy were identified during the study period. Two hundred fifty cases were matched to 722 controls. Of the cases, 68 (27.2%) had received the intranasal vaccine compared with 8 (1.1%) of the controls, leading to an adjusted odds ratio of 84.0 (95% CI 20.1–351.9). In this study, there was no increased risk of Bell's palsy after receipt of the parenteral vaccine: OR 1.1 (9%CI 0.6–2.0). The peak onset interval of Bell's palsy after the intranasal vaccination was 31–60 days. These findings led Berna Biotech to withdraw that product permanently [300]. Since this finding, there has been interest in determining whether or not other influenza vaccines cause Bell's palsy.

Two phase I vaccine trials, one of intranasal *Mycobacterium tuberculosis* antigen and the second, an HIV antigen both adjuvanted with modified *E. coli* heat labile toxin were halted when 1 of 9 recipients of the adjuvanted *M. tuberculosis* vaccine recipients and 1 of 20 of the subjects in the adjuvanted arms of the HIV vaccine trial developed Bell's Palsy [301]. *E. coli* LT and cholera toxins are actively

taken up by peripheral nerves and undergoes retrograde axonal transport by binding neuronal gangliosides [299,302]. Subsequent studies in mice, although not in other species, found endotoxin in the olfactory bulb after intranasal installation [303]. The most likely hypothesis for the association with all three vaccines and Bell's palsy is that the *E. coli* enterotoxin resulted in inflammation and entrapment of the facial nerve in the facial canal [301].

5.11.3. Case reports

Individual reports of Bell's palsy after currently licensed IIV have been made [304], including a recent report of a 9 year old boy with isolated left facial nerve palsy 9 days after receipt of the H1N1 pandemic influenza vaccine [305]. MRI of the brain in this case revealed enhancement of both internal auditory canals and facial nerves, right greater than left. Other than a temporal association with vaccination, these cases do not provide additional evidence for a causal relationship.

5.11.4. Population-based studies

Reports of Bell's palsy to VAERS in the US after IIV from 1991 to 2001 revealed a signal of possible increased number of Bell's palsy reports the first month after IIV vaccination in all age groups, greatest for those >65 years and 40% of the 154 cases reported occurred within 1–3 days after vaccination [400]. However, population-based studies of Bell's palsy after influenza vaccination found no association [70,291,306]. A VSD analysis over 3 seasons (2005–2008) in which 1.2 million doses of IIV were given to children and 4.7 million were given to adults found no increased signal of Bell's palsy after vaccination [306]. Claims-based data after H1N1 (both inactivated and live) vaccination of over 500,000 people in a large insurer revealed that, in the first 42 days after vaccination compared with days 43–84 after vaccination, there was an incident rate ratio (IRR) for Bell's palsy in all ages 1.16 (95% CI 0.75–1.84) [291]. Analysis of nearly 1 million seasonal IIV recipients also showed no increased risk of Bell's palsy in that population [IRR 0.83 (95% CI 0.60–1.15)] [291]. PRISM (FDA Postlicensure Rapid Immunization Safety Monitoring) data also looking at H1N1 inactivated vaccination with or without seasonal vaccine (over 3 million doses) showed an IRR of 1.21 (99% CI: 0.54–2.69) in persons 6 months to 24 years of age, and 1.23 (99% CI: 0.88–1.73) in those ≥25 years [307]. When those who had received only pandemic H1N1 vaccine were analyzed, the rate was not significant for persons ≤24 year olds, however those ≥25 years of age had an IRR of 1.65 (99%CI 1.03–2.64; $p = 0.006$). The authors cautioned that findings might have been confounded by seasonal differences in rates. No clusters of timing after immunization were found using the temporal scan statistic. In addition, corrections for multiple comparisons were not made in these analyses. A self-controlled case series of a large database in the United Kingdom (the General Practice Research Database) identified 2263 episodes of Bell's palsy between 1992 and 2005. The relative incidence of Bell's palsy was 0.97 (95% CI: 0. 84–1.13) for onset 1–91 days after vaccination compared to control periods [401].

The VSD was also used to monitor the safety of seasonal and pandemic (H1N1) 2009 vaccines during the 2009–10 influenza season using a self-controlled study design with variable risk windows for signal detection of 11 different disease outcomes [402]. Since multiple outcomes were tested at weekly intervals for four different vaccines, sequential statistical testing was used to adjust for multiple testing. All age groups were monitored, and more than 4.5 million doses of vaccine were administered (1,345,663 H1N1 inactivated vaccine, 267,715 H1N1 live attenuated vaccine, 2,741,150 seasonal IIV, and 157,838 LAIV). The coverage rates for seasonal vaccines was 81% for children 6–23 months of age, 56% for those 24–59 months of age, 36% for children 5–17 years of age. Coverage rates for the pandemic (H1N1) 2009 vaccines were somewhat lower [402]. No signals were detected in children for any of the outcomes. For adults 25 years of age and older, a signal was detected for Bell's palsy following the inactivated pandemic (H1N1) 2009 vaccines, but not for the other vaccines. There was no evidence of temporal clustering; adjusting for seasonality using a case-centered logistic regression analysis revealed an odds ratio of 1.26 (95% CI: 0.97–1.63) for adults. Seasonality has been observed for Bell's palsy in other populations. Chart reviews to confirm cases were not performed. The authors noted that in a previous study using the VSD, only 72% of reported cases of Bell's palsy were confirmed after chart review [402].

For the MF59-adjuvanted pandemic (H1N1) 2009 vaccines (Focetria, Novartis), in passive reporting from the EU, no significant difference in facial palsy reports were submitted as compared to reports following a non-adjuvanted seasonal vaccine [70].

5.11.5. Summary

Although some signals suggested the possibility of an increased risk of Bell's palsy, the available evidence does not indicate an increase in adults and the overall evidence does not support an increased risk in any age group.

5.12. Immune thrombocytopenia (ITP) or immune thrombocytopenic purpura

Immune thrombocytopenia (ITP) is currently the preferred term for diseases that were previously called idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura [308]. For the purposes of this review, we will use the acronym ITP to refer to all three names that have appeared in the literature. ITP is usually defined as the development of a platelet count less than $100 \times 10^9\ L^{-1}$ in the absence of other causes or diseases that may cause thrombocytopenia [308]. Most pediatric patients present with petechiae and no or mild bleeding; rarely severe bleeding occurs, but children with ITP are at increased risk of significant bleeding from mild trauma [309]. The majority of patients with ITP have autoantibodies directed against receptors on the platelet surface [310].

5.12.1. Causal factors

Most pediatric patients have a preceding respiratory illness and the pathogenesis is assumed to involve development of cross-reacting antibodies stimulated by the infection. Measles-containing vaccines are a recognized cause of ITP [311]. Transient decreases in platelet counts are observed in most children within a few days after receiving measles vaccine, presumably because of a direct interaction between the measles vaccine virus and circulating platelets [312]. Several population-based studies have documented an increased risk of ITP and a meta-analysis of 12 studies indicates a rate of 2.6/100,000 children receiving a first dose of measles-containing vaccines [311,313,403–405]. The pathogenesis appears to involve the measles vaccine virus attachment to platelets and stimulation of antibodies that cross react with platelet surface antigens.

5.12.2. Case reports

Case reports of new onset ITP following influenza immunizations stimulated speculation that these vaccines might also stimulate cross-reacting autoimmune response and cause ITP [311,314–316]. There are also reports of relapses of ITP associated with TIV [316].

5.12.3. Epidemiologic studies

None of the controlled epidemiologic studies reviewed identified a significant association between influenza vaccines and ITP. In a case–control study in France involving 224 incident cases of ITP

in persons ≥15 years of age, 20% of cases and 26% of controls had received influenza vaccines in the preceding 12 months (OR 0.66, 95% CI: 0.45–0.98) [317].

Self-controlled case series methods have been used to assess the risk of ITP following influenza vaccines in several populations using the 42 days following vaccines as a risk window. In a health plan in the United States where 3.1 million persons of all ages received seasonal influenza vaccines between 2006 and 2009, there was no evidence of an increased risk of ITP following vaccine as compared to the pre-vaccination control window (IRR = 0.74, 95% CI: 0.42–1.31) or the post-vaccination control window (IRR = 0.78, 95% CI: 0.43–1.40) [406]. In Taiwan, 3.5 million doses of pandemic H1N1 influenza vaccines were administered; the incidence of ITP was not significantly different in the risk vs. control windows for influenza vaccines without an adjuvant (IRR = 1.09, 95% CI: 0.65–1.85) or for vaccines containing the MF59 adjuvant (IRR = 0.56, 95% CI: 0.13–2.36) [241]. In a population of 1.8 million children <18 years of age who participated in a managed care organization in the United States, 197 chart confirmed cases of ITP were identified in 2000–2009 [313]. No significantly elevated risks were identified following TIV, but this study did confirm the elevated risk associated with MMR (IRR = 5.48, 95% CI: 1.61–18.64). A 2009–2010 retrospective cohort study in northern Italy matched 103,642 persons (12,447 0–17 years of age) who received an MF59-adjuvanted pandemic H1N1 vaccine with an equal number of controls [318]. There was no evidence for an increased risk of ITP (OR of 1.0) in the 6 weeks following vaccination. Also, there was no elevated risk of ITP during the six weeks following influenza vaccines with the MF59 adjuvant or without an adjuvant among persons 65 years of age or older.

There was no increased risk of ITP among 2.1 million veterans in the United States in the 42 days following influenza vaccines in 2010–2011 as compared to later times using a self-controlled case series method (IRR = 0.71, 95% CI: 0.32–1.59) [319].

5.12.4. Summary

Epidemiological evidence from different studies by different investigators in different populations, consistently reveals no increased risk of ITP associated with influenza vaccines.

5.13. Other disorders

There are case reports of other disorders following influenza vaccines involving different organ systems including pericarditis, venous thrombosis, myocardial infarctions, stokes, etc. However, this review did not identify sufficient epidemiologic or other data to justify in depth reviews of these topics.

6. LAIV and LAIV-L

6.1. Brief history of live attenuated influenza vaccines and safety issues

Safety concerns that have been raised about live attenuated influenza vaccines include fever, respiratory infections or symptoms, wheezing, increased hospitalizations, and use in individuals with underlying conditions, including immunosuppression and asthma. Pre-licensure studies in the development of live vaccines utilized different cold-adapted strains for the backbone virus [320]. These backbones were not consistently attenuated or were genetically unstable [320]. When tested in humans, some were unacceptably reactogenic. The A/Mallard/6750/78 avian-human cold-adapted backbone was found to have unacceptable reactogenicity in children. An H1N1 monovalent vaccine with A/Kawasaki/86 on the Mallard backbone was tested in children 6–48 months of age in a dose-escalating trial. The avian-human strain caused greater febrile reactions than did the A/Ann Arbor strain or placebo. The children who received the Mallard vaccine were also more likely to have upper respiratory tract or influenza-like symptoms and otitis media than were the children in the other groups [407]. Eventually, cold-adapted, temperature-sensitive backbones were developed which were genetically stable and sufficiently attenuated yet effective in protecting against influenza infection and disease. In the United States, Canada, Israel and Europe, the backbone for the influenza A virus in LAIV (FluMist® and Fluenz®) is the A/Ann Arbor/6/60 (H2N2) strain and for the B viruses it is the B/Ann Arbor/1/66. In Russia, the cold-adapted strains are A/Leningrad/134/47/57 (H2N2) and B/USSR/60/69 [321]. Much of the English language literature about LAIV safety is based on the Ann Arbor backbones. The term LAIV is used in this document to represent the vaccine made on the Ann Arbor backbones. The live vaccine using the Leningrad and USSR backbones is referred to as LAIV-L.

6.2. Preferential use and restrictions for use of LAIV

Live attenuated influenza vaccine (LAIV) has been shown to be very effective at preventing influenza illness in children, and may be more effective than inactivated vaccine in young children [158,322,323]. Health agencies from several countries and jurisdictions recommend LAIV as the preferred vaccine for eligible children 2–8 years of age [324,325,326]. This recommendation is tempered by the restrictions for the use of LAIV in children with some underlying conditions which vary by country. In February 2015, the ACIP removed the preference for LAIV because of inconsistency in vaccine effectiveness in the previous two years. In the United states, LAIV "should not be used" in children 2–4 years with a history of wheezing or asthma in the 12 months prior to vaccination, and there is a precaution for use in persons of any age with asthma who might be at increased risk for wheezing after LAIV because of the concern for worsening symptoms after vaccination ([50], FluMist® package insert). Also, LAIV should not be used in persons with underlying medical conditions that might put them at increased risk (chronic pulmonary, cardiovascular, renal, hepatic, neurologic, or metabolic disorders, or anyone with an egg allergy) primarily due to a lack of data in these populations, rather than known increased risk for adverse events.

In the UK, LAIV is preferred and indicated for children 2 to <18 years of age except those with active wheezing (within 7 days), on oral steroids, or high dose inhaled steroids. LAIV is also contraindicated in persons with severe immunodeficiency from HIV, malignancy, primary immunodeficiency or immunosuppressive therapy [325]. In Canada, the National Advisory Committee on Immunization (NACI) recommends LAIV preferentially over TIV in children and adolescents 2–17 years old. Children with stable, non-severe asthma are also included in the recommended category. In children with chronic illness, with the exception of immune compromise or severe asthma, there is no preference for LAIV or TIV because of lack of evidence (http://www.phac-aspc.gc.ca/naci-ccni/flu-grippe-eng.php#v).

6.3. Adverse events following LAIV

Vaccine virus shedding following LAIV is inversely correlated with age; young children are the most likely to shed virus and for the longest time [327,328,329]. The majority of young children who receive LAIV shed the vaccine virus for several days; in 9–36 month olds, viral shedding continues for a mean of 7.6 days [328].

In general, the rate of attributed adverse events after LAIV decreased with increasing age [158,327,330]. The most frequently reported adverse event after LAIV administration in any age group was coryza. In early trials of LAIV, more respiratory symptoms

were noted after LAIV than after inactivated vaccine or controls [331]. Rates of rhinorrhea varied from 26% in vaccinees of all ages to 80% in young children compared with rates in placebo recipients of 19–75% in the same studies 154,158,211,322,328,331–333]. Increased rates of rhinorrhea are most significant in days 2 and 3 after vaccination, but are still higher than in controls at 8 or 9 days after vaccination [330]. Although rhinorrhea has been related to shedding, there is not a strong correlation between vaccine virus shedding and respiratory symptoms after vaccination [327]. An integrated analysis was performed of data from 20 controlled studies with LAIV in children 2–17 years of age (including many of the studies discussed individually in this review) [334]. In the studies that compared TIV, 4108 children who received LAIV were compared with 4118 TIV recipients. In the placebo-controlled studies, the numbers were 3245 LAIV recipients and 1994 placebo recipients. In the TIV controlled study, the most common reactogenicity event among LAIV recipients compared to TIV recipients was runny/stuffy nose (rate difference 11.8% after dose 1 and 4.2% after dose 2 ($p < 0.01$) [334]. No other reactogenicity event assessed was greater in the LAIV recipients than the TIV recipients. In the placebo controlled studies, after dose 1 LAIV recipients had more runny/stuffy nose (rate difference 6.8%, $p < 0.01$), headache (rate difference 6.9%, $p = 0.02$), and tiredness/decreased activity (rate difference 2.1% $p = 0.03$). These adverse events decreased with subsequent vaccinations [334].

6.3.1. Fever

It is not clear whether there is an increased risk of fever in LAIV recipients. An early trial of bivalent LAIV vs. IIV and control in 5210 persons ages 1–65 years over 5 seasons (1985–1990; in which 12,500 doses were given) showed that LAIV did not cause more fever than IIV or placebo [331]. The authors did not break the data down by age or year of vaccination but did note that reaction rates were comparable for different age groups and did differ by year. Later trials in children [158,330,332] showed an increase in fever rates on day 2 after vaccination compared with placebo [6.5% vs. 1.6% ($p < 0.001$) [332]; OR 5.23 (95% CI: 2.48–11.0) [330]]. A placebo-controlled multicenter study of LAIV vs. placebo in 8 Asian regions between 2000 and 2003 randomized over 3000 children ages 12–35 months to LAIV or placebo [211]. One thousand nine hundred children received at least 1 dose (and up to 3 doses over 2 years) of LAIV. Fever (defined as $\geq$37.5 °C) occurred in 22.0% of vaccinees and 17.6% of placebo recipients in the 11 days after the first dose ($p = 0.004$). There was no difference in rates of fever $\geq$38.6 °C (4.9% LAIV, 4.1% placebo ($p = 0.323$) after dose 1) [211]. This increase in fever rates was seen after the first dose of vaccine and the risk was lessened or absent in subsequent doses [158,211] and in subsequent years with different vaccine components [330]. Other studies in children as young as 6 months did not find increased risk of fever due to LAIV [328,322,323,335]. In the integrated analysis, which looked at reactogenicity in children 2–17 years of age, no statistically significant increase in fever was found in LAIV vs. TIV or LAIV vs. placebo. Importantly, this analysis did not subdivide the children by age, and there may have been differences in rates for different age groups [334].

6.3.2. Wheezing following LAIV

Interest in whether LAIV vaccines can cause wheezing stems from the fact that influenza virus infections have been associated with wheezing in young children [336,337]. Although the mechanisms involved in influenza infection causing wheezing are not completely understood, the pathophysiology is thought to involve inflammatory cytokines [338–340] and perhaps virus-induced inflammasome activation [341]. Theoretically, the same mechanisms that could lead wild-type influenza viruses to cause wheezing could be involved in the pathophysiology of LAIV-induced wheezing. However, the attenuated vaccine virus is temperature sensitive and therefore should not be replicating in the lower respiratory tract.

Several studies have looked at the potential risk of wheezing after LAIV in children <2 years of age [154,158,211,335,342,343], with most finding no increased risk of wheezing after vaccination. Two large studies in young children have shown that LAIV was associated with small, but not significantly, higher rates of wheezing. A large multi-country (US, 12 countries in Europe and the Middle East, 3 countries in Asia) double-blind, randomized trial was conducted in 8475 children 6–59 months of age. The rate of medically-attended wheezing in the 6 weeks after vaccination in children under 12 months of age who received LAIV compared to children who received IIV was 3.8% vs. 2.1% ($p = 0.076$) [158]. No difference was seen in any other age group. For all children under 24 months, 3.2% of LAIV recipients and 2.0% of TIV recipients had medically-attended wheezing (adjusted difference of 1.18 (95% CI: 0.13–2.29) [158]. In another study of 9689 children 1–18 years of age randomized 2:1 to receive LAIV vs. placebo, a higher level of "asthma events" was found in 18–35 month-old children who received LAIV compared with placebo recipients (RR 4.06 90% CI: 1.29–17.86) [342]. This increased risk occurred throughout the 42-day observation period was not related to the timing of immunization, and was not seen in other age groups. That study used confidence intervals of 90%; if the data were reanalyzed using a traditional 95% CI, the relative risk would not be statistically significant (95% CI: 0.36–23.72) [221]. Of interest, 44% of the children 18–35 months old who had "asthma" after vaccination had a previous history of reactive airway disease [342]. For children of all ages (1–18 years) in this study who had a previous history of asthma/reactive airway disease, there was no increased risk, suggesting that the risk, if any, was limited to the youngest recipients. In a subset analysis of the children with wheezing from one of the sites in the Belshe study, the primary risk factor for wheezing after vaccination was a family history of asthma, suggesting a genetic predisposition for wheezing [344].

Several studies of LAIV in children over 2 years of age have not found a signal for increased wheezing after LAIV [156,158,342]. A prospective observational study of over 82,000 children 24–59 months of age over 3 years showed no increase in asthma or wheezing in children who received LAIV ($n = 28,226$ receiving 33,433 doses) compared with 3 different controls (within-cohort controls (self-controlled risk interval analysis), matched concurrent unvaccinated controls and matched concurrent TIV-vaccinated controls) [345]. Hospitalization for wheezing and asthma was lower in the LAIV vs. TIV recipients [345]. A non-randomized open label community-based trial of LAIV conducted over 4 years in 11,000 children 18 months to 18 years [346] found no overall increase in wheezing or asthma. In a subanalysis, children 18 months to 4 years had a marginally significant increase wheezing during the first year on days 15–42 after vaccination (RR 2.85; 95% CI: 1.01–8.03). However, this finding was not seen in the subsequent 3 years [year 2, identical vaccine, RR 1.42 (95% CI: 0.59–3.42); year 3 RR 0.47 (95% CI: 0.122–1.83), year 4 RR 0.20 (95% CI: 0.03–1.54)], and the authors noted it was likely due to chance as they had not corrected for multiple comparisons [346]. Children were grouped 18 months to 4 years, so it is not possible to determine if wheezing after LAIV was greater in those younger than 2 years of age. The integrated analysis of LAIV trials in children (which included data from several of the studies mentioned above) found no increase in wheezing or lower respiratory symptoms in either children 2–17 years of age or in the subset of children 24–35 months of age [334]. Post-licensure surveillance of VAERs and other systems have not identified any greater than expected reports of asthma or wheezing after LAIV [74,156,159,160].

6.3.3. LAIV in children with wheezing or asthma

Early studies of LAIV safety demonstrated that rates of wheezing after LAIV were higher in children with a history of asthma or recurrent wheezing than in those without that history [158,342]. These results led to advisory committee recommendations cautioning against using LAIV in children <5 years who had at least one episode of wheezing within the last 12 months [50]. Subsequently, several studies sought to determine the safety of LAIV in children with a history of asthma or wheezing. When compared to either IIV recipients or placebos, there was no difference between the rates of medically attended wheezing after either LAIV or IIV in children older than 2 years with a history of asthma or recurrent wheezing [158,322,323,347,348]. No difference was noted in FEV1, FVC, or FEF between vaccinees and placebo recipients after vaccination or as compared with baseline [347]. In addition, there were no significant differences in asthma symptom scores, nighttime awakening or mean PEFR in 6–17 year olds with asthma who received LAIV [322]. Retrospective analysis of health claim data in children <5 who received LAIV despite having contraindications showed no increase in hospitalizations in the children who received LAIV compared with those receiving TIV over several seasons [159,160]. A multicountry European study found no difference in rates of wheezing between LAIV and TIV recipients (9.3% and 9.9% in the 42 days after the first dose, respectively) in children 6–71 months of age with a history of recurrent respiratory tract infections [323].

6.3.4. LAIV in children with underlying conditions

LAIV has generally been found to be well tolerated in the relatively small numbers of children with underlying medical problems for whom the vaccine is not recommended. LAIV was given to 24 mildly immunocompromised HIV infected children 1–7 years of age [349] with no difference in safety signals when compared to placebo in a crossover design. A larger study of LAIV vs. IIV in 243 HIV infected children 5–18 years of age on highly active antiretroviral therapy also found no increase in adverse events in the LAIV recipients compared with the IIV recipients [350]. Two small studies have examined LAIV in children with cancer who had mild-moderate immunosuppression [237,351]. In one study, 28 LAIV recipients were compared to 27 TIV recipients [237] and in the other, 20 subjects were randomized to LAIV or to placebo during the influenza off-season [351]. Other than more rhinorrhea and congestion, the children who received LAIV did not have significantly more adverse events than the comparator groups. Also, they did not shed LAIV virus (as determined by viral culture and PCR) longer than would be expected (maximum of 7 and 10 days after vaccination) [237,351]), which is comparable to shedding in healthy children [327].

A recent study in 168 children 2–18 years of age with cystic fibrosis followed children for 56 days after LAIV. Comparing the "at-risk" period (days 0–28 after vaccination) with the non-at-risk time window (days 29–56 following LAIV). The LAIV recipients did have a greater incidence of mild wheezing after LAIV, especially on the day of vaccination, than in the control period, but no significant difference in respiratory deteriorations or hospitalization was found between the time periods [352].

6.3.5. LAIV and hospitalizations

A post hoc analysis of the data in the large multi-country study [158] revealed an increased risk for hospitalization from all causes in LAIV recipients over the 6 months following vaccination for children 6–11 months of age regardless of prior history of wheezing (6.1% vs. 2.6% in the IIV group $p = 0.002$). There was also an increased risk for hospitalization from all causes in children 1–4 years of age who had a previous history of wheezing at the time of immunization. The differences for each individual year were not statistically significant. For children without a history of wheezing, the rates of hospitalization were lower for LAIV recipients over 1 year of age; and for all children over 4 years of age the rates of hospitalization were lower for LAIV recipients, presumably because of better prevention of influenza in LAIV recipients [158]. Other studies have not found an increase in hospitalizations after LAIV but most have not studied as many children under 2 years of age.

6.3.6. Other adverse events

For other adverse events after LAIV in children, there is less consistency among studies. While some studies described decreased activity levels or irritability in children after LAIV [211,330–332], others found no difference in the rates [154,328,323,335]. Other studies have been inconsistent regarding gastrointestinal symptoms such as decreased appetite or nausea. It is unclear if these symptoms are attributable to the vaccine or whether the methods of adverse event monitoring or patient populations studied can explain the differences in findings. One multi-country randomized placebo controlled study (South Africa, Brazil and Argentina) of LAIV in 3200 vaccine naïve children age 6–36 months found no increase in any adverse events between LAIV and placebo group, including fever, activity level and rhinorrhea. They did note that the recipients of LAIV had less cough than the placebo recipients (50.3% vs. 8.2% $p < 0.004$) [335]. The study done in Asian countries also found that LAIV recipients had less cough after the first (but not subsequent) dose (34.1% vs. 38.6% $p = 0.010$) [211].

6.4. Concomitant administration of LAIV with other vaccines

Few studies have examined adverse events after LAIV co-administered with another childhood immunizations. A multinational study from 7 countries in Asia and South America enrolled 2166 children age 6 to <36 months who received either LAIV with OPV, placebo plus OPV or LAIV alone [343]. No differences in fever or cough rates were found between the three groups except for an increase in fever $\geq$40 °C axillary in the placebo plus OPV group compared with the LAIV groups (0.5% vs. 0%, $p = 0.037$). There was an increase in runny nose and nasal congestion in the LAIV groups: 70% in LAIV + OPV; 67.2% in LAIV group alone vs. 62.7% in the OPV group after the first dose ($p = 0.006$) [343]. A second multicenter phase III study in 13 countries in Asia, Europe and Central America administered LAIV or placebo with measles, mumps and rubella vaccine (MMR) to 1233 children 11 to <24 months of age [154]. After the first dose, the children who received both vaccines were more likely to have fever >37.5 °C axillary than the children who received placebo and MMR (49.9% vs. 41.7%, $p = 0.009$), but there were no differences in the rates of fever >38.6 °C or $\geq$40 °C. Children who received LAIV and MMR vaccines together were also more likely to have runny nose or nasal discharge (70% vs. 51.6%, $p < 0.001$) and to use antipyretics (37.7% vs. 29.2% $p = 0.004$) than were children receiving placebo and MMR [154].

A US and Australian trial in 1251 children 12–15 months of age compared children randomized to receive MMR, varicella and LAIV vaccines with children who received MMR and varicella vaccines plus placebo, or LAIV alone [100]. Children who received LAIV with MMR and varicella vaccines were more likely to have fever in the subsequent 10 days than those who received LAIV alone (>100 °F oral 51.7% vs. 29.1%; >101 °F 29.4% vs. 13.9% and >102 °F 16.3% vs. 7.7%). Recipients of all 3 vaccines had no increased rates of wheezing as compared to LAIV only recipients (0.2% vs. 1.3%). Children who received all 3 vaccines were also more likely to be irritable than LAIV only recipients (60.4% vs. 51.5%). In the 42 days after vaccination children who received all 3 vaccines were more

likely to have runny nose and congestion than those who received MMR and varicella vaccines plus placebo (84% vs. 77.6%), and there was no significant difference in rates of wheezing (1.2% vs. 2.5%) [100].

6.5. Quadrivalent LAIV

The US Food and Drug Administration licensed a quadrivalent LAIV in 2012 and the first doses were available in the 2013–14 influenza season. In healthy children 2–17 years of age, most adverse events following quadrivalent LAIV were similar to those experienced following trivalent LAIV [107]. A small increase in fever was noted in children 2–8 years of age after the first dose; 5.1% of quadrivalent LAIV recipients had fever ≥38 °C, compared with 3.1% of trivalent LAIV recipients ($p = 0.04$). There was also a slight increase in fever >39 °C (1.2% vs. 0.3%, $p = 0.04$) in the quadrivalent group. An analysis of the VAERS and VSD data comparing the 2013–2014 influenza season (quadrivalent LAIV) and 2012–2013 season (trivalent LAIV) found no new safety concerns in children [408].

6.6. LAIV-L

Far less English language literature exists on the safety of LAIV-L. Early studies of 337 children comparing the LAIV-L to inactivated whole virion vaccine or placebo showed that adverse events in the 3 groups were similar [353]. A larger study in 34 schools (>12,000 children 7–14/years of age) over 2 years compared the efficacy of LAIV-L to whole virion inactivated virus vaccine and placebo. A subset of >100 children/group was identified for reactogenicity assessment for 7 days after vaccination. In the first year for the 7–10 year olds, 1/162 LAIV-L recipients had a low-grade fever (37.5–38.5 °C), the following year, 2/323 LAIV recipients, 2/278 placebo recipients and 5/271 inactivated vaccine recipients had low grade fever [321]. A large study comparing mono-, bi- or trivalent-LAIV-L to placebo in 130,000 children ages 3–14 years was performed in Russia and Cuba between 1986 and 1991. In the subset of 1366 children assessed for safety there was no significant increase in adverse events in the LAIV-L recipients over placebo recipients in either the 3–6 or 7–14 years of age groups [354]. This LAIV-L was also shown to be effective in preventing influenza like illness in children, and perhaps, more effective than the IIV [321].

An H1N1 based LAIV-L (Nasovac®) made in India was evaluated in retrospective post-marketing survey of 7565 people 3–85 years of age approximately 1 year after the vaccine was administered [355]; 81 adverse events were reported in 49 individuals. Runny nose was reported in 0.32% and was the most commonly reported symptom [355].

Recent phase 2 and phase 3 studies of LAIV-L made by the Serum Institute of India, Ltd involving more than 2000 children 24–59 months old in Bangladesh, found no increased risk of wheezing, despite the fact that more than ¼ of the children had been previously treated for asthma or wheezing (Ortiz, Brooks (manuscripts in revision, Vaccine)). In the phase 3 study, LAIV-L recipients were less likely to have wheezing from Day 43–6 months after vaccination as compared to placebo recipients (3.3% vs. 5.5%, risk difference −1.87 (95% CI −4.23, −0.3; $p = 0.039$). Systemic adverse events, primarily tachypnea and subjective fever, were observed in 37.7% of LAIV-L recipients and 30.3% of placebo recipients ($p = 0.002$). Tachypnea was greater in 2 and 4 year-olds who received LAIV-L, but not in 3 year olds. Also, in the 2 year olds, local reactions following LAIV-L were reported in 30.9% vs. Placebo 21.5% ($p = 0.021$), primarily an increase in runny nose/nasal congestion. There was no difference in hospitalizations in the 6 months after receipt of LAIV or placebo (Brooks manuscript in revision, Vaccine).

6.6.1. Conclusions

In conclusion, LAIV and LAIV-L are well tolerated in children. The most common adverse events are transient symptoms of stuffy nose or rhinorrhea. Fever may also be increased as compared to placebo in younger children. In children 2 years of age and older, the majority of studies reveal no increased rates of wheezing. The data on LAIV use in children less than 2 or those with underlying health conditions is limited, and these vaccines are not recommended for those populations. Studies of wheezing in children <2 year of age are inconsistent. Most studies of LAIV and LAIV-L in children have not shown increased risks of hospitalization. Most children with underlying asthma/wheezing or other chronic medical problems reveal no clinically significant increased rates of adverse events. More studies are needed in children less than two years of age and in children living in low and middle-income countries. These studies should include follow-up periods long enough to ascertain whether there is an increased risk of hospitalization in young children and children with prior wheezing or asthma. No long-term studies of the impact of wheezing episodes in LAIV or LAIV-L recipients have been conducted.

7. Summary and conclusions

In summary, most influenza vaccines are generally safe, but influenza vaccines can cause rare serious adverse events. Some adverse events, such as fever and febrile seizures, are more common in children than adults. There can be differences in the safety of vaccines in different populations due to underlying differences in genetic predisposition to the adverse event. Live attenuated vaccines have not been studied adequately in children under 2 years of age to determine the risks of adverse events; more studies are needed to address this and several other priority safety issues with all influenza vaccines in children. All vaccines intended for use in children require safety testing in the target age group, especially in young children. Safety of one influenza vaccine in children should not be extrapolated to assumed safety of all influenza vaccines in children. The low rates of adverse events from influenza vaccines should not be a deterrent to the use of influenza vaccines because of the overwhelming evidence of the burden of disease due to influenza in children.

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Appendix 1. Systematic literature search terms

Influenza Vaccines (included with all searches using "AND" term)

PubMed: Version 1 (V1)

((“influenza vaccines”[Mesh]) OR ((“Vaccination”[Mesh] OR vaccinations OR vaccination OR “Vaccines”[Mesh] OR “Viral Vaccines”[Mesh] OR vaccine OR vaccines OR “Immunization”[Mesh] OR Immunization OR Immunizations OR Immunisation OR Immunisations OR immunized OR immunised OR immunize OR immunise) AND (“influenza, human”[Mesh] OR influenza OR flu OR influenzavirus)))

EMBASE: V1

((‘influenza vaccination’/exp OR ‘influenza vaccine’/exp) OR ((‘influenza’/exp OR influenza OR influenzavirus OR flu) AND (vaccine OR vaccines OR vaccination OR vaccinations OR immunization OR immunizations OR immunisation OR immunisations OR immunized OR immunised OR immunize OR immunise)))

((TITLE-ABS-KEY(influenza OR influenzavirus OR flu) AND TITLE-ABS-KEY(vaccine OR vaccines OR vaccination OR vaccinations OR immunization OR immunizations OR immunisation OR immunisations OR immunized OR immunised OR immunize OR immunise)))

PubMed: Version 2 – Refined (V2)

((“influenza vaccines”[Mesh]) OR ((“Vaccination”[Mesh] OR “Vaccines”[Mesh] OR “Viral Vaccines”[Mesh] OR “Immunization”[Mesh]) AND “influenza, human”[Mesh]) OR (“influenza vaccine” OR “influenza vaccines” OR “influenza vaccination” OR “influenza vaccinations” OR “influenza vaccine” OR “influenza immunization” OR “influenza immunizations” OR “influenza immunisation” OR “influenza immunisations” OR “flu vaccine” OR “flu vaccines” OR “influenzavirus vaccine” OR “influenzavirus vaccines” OR “flu vaccination” OR “flu vaccinations” OR “influenzavirus vaccination” OR “influenzavirus vaccinations” OR “flu immunization” OR “flu immunizations” OR “flu immunisation” OR “flu immunisations” OR “influenzavirus immunization” OR “influenzavirus immunizations” OR “influenzavirus immunisation” OR “influenzavirus immunisations”)

EMBASE:V2

((‘influenza vaccination’/exp OR ‘influenza vaccine’/exp) OR (‘influenza vaccine’ OR ‘influenza vaccines’ OR ‘influenza vaccination’ OR ‘influenza vaccinations’ OR ‘influenza immunization’ OR ‘influenza immunizations’ OR ‘influenza immunisation’ OR ‘influenza immunisations’ OR ‘flu vaccine’ OR ‘flu vaccines’ OR ‘flu vaccination’ OR ‘flu vaccinations’ OR ‘flu immunization’ OR ‘flu immunizations’ OR ‘flu immunisation’ OR ‘flu immunisations’ OR ‘influenzavirus vaccine’ OR ‘influenzavirus vaccines’ OR ‘influenzavirus vaccination’ OR ‘influenzavirus vaccinations’ OR ‘influenzavirus immunization’ OR ‘influenzavirus immunizations’ OR ‘influenzavirus immunisation’ OR ‘influenzavirus immunisations’))

GBS

PubMed (247 results):

(“Guillain-Barre Syndrome”[Mesh] OR “Guillain Barre” OR “Guillain-Barre” OR “Guillain-Barré Syndrome” OR “Guillaine-Barre Syndrome” OR “Guillaine Barre Syndrome” OR “Landry-Guillain-Barre Syndrome” OR “Landry Guillain Barre Syndrome” OR “Miller Fisher Syndrome”[Mesh] OR “Miller Fisher Variant” OR “Miller-Fisher Syndrome” OR “Miller Fisher Syndrome” OR “Fisher Syndrome” OR “Acute Inflammatory Polyneuropathy” OR “Acute Inflammatory Polyneuropathies” OR “Acute Inflammatory Demyelinating Polyneuropathy” OR “Acute Inflammatory Demyelinating Polyradiculoneuropathy” OR “Acute Inflammatory Polyradiculoneuropathy” OR “Acute Inflammatory Polyradiculoneuropathies” OR “Acute Inflammatory Demyelinating Polyradiculoneuropathy” OR “Acute Inflammatory Demyelinating Polyradiculoneuropathies” OR “Acute Autoimmune Neuropathy” OR “Acute Autoimmune Neuropathies”)

EMBASE (858 results):

(‘guillain-barre syndrome’/exp OR ‘guillain barre’ OR ‘guillain-barre’ OR ‘guillain-barré syndrome’ OR ‘guillaine-barre syndrome’ OR ‘guillaine barre syndrome’ OR ‘landry-guillain-barre syndrome’ OR ‘landry guillain barre syndrome’ OR ‘miller fisher variant’ OR ‘miller-fisher syndrome’ OR ‘miller fisher syndrome’ OR ‘fisher syndrome’ OR ‘acute inflammatory polyneuropathy’ OR ‘acute inflammatory polyneuropathies’ OR ‘acute inflammatory demyelinating polyneuropathy’ OR ‘acute inflammatory polyradiculoneuropathy’ OR ‘acute inflammatory polyradiculoneuropathies’ OR ‘acute inflammatory demyelinating polyradiculoneuropathy’ OR ‘acute inflammatory demyelinating polyradiculoneuropathies’ OR ‘acute autoimmune neuropathy’ OR ‘acute autoimmune neuropathies’)

Scopus (807 results):

((TITLE-ABS-KEY(“Guillain Barre” OR “Guillain-Barre” OR “Guillain-Barré Syndrome” OR “Guillaine-Barre Syndrome” OR “Guillaine Barre Syndrome” OR “Landry-Guillain-Barre Syndrome” OR “Landry Guillain Barre Syndrome”) OR TITLE-ABS-KEY(“Miller Fisher Variant” OR “Miller-Fisher Syndrome” OR “Miller Fisher Syndrome” OR “Fisher Syndrome”) OR TITLE-ABS-KEY(“Acute Inflammatory Polyneuropathy” OR “Acute Inflammatory Polyneuropathies” OR “Acute Inflammatory Demyelinating Polyneuropathy” OR “Acute Inflammatory Demyelinating Polyradiculoneuropathy”) OR TITLE-ABS-KEY(“Acute Inflammatory Polyradiculoneuropathy” OR “Acute Inflammatory Polyradiculoneuropathies” OR “Acute Inflammatory Demyelinating Polyradiculoneuropathy” OR “Acute Inflammatory Demyelinating Polyradiculoneuropathies”) OR TITLE-ABS-KEY(“Acute Autoimmune Neuropathy” OR “Acute Autoimmune Neuropathies”)))

Febrile seizures

PubMed (94 results):
("seizures, febrile"[MeSH Terms] OR (("fever"[MeSH Terms] OR "fever"[All Fields] OR "fevers"[All Fields] OR "febrile"[All Fields] OR "pyrexia"[All Fields] OR "pyrexial"[All Fields] OR "pyrexias"[All Fields] OR "hyperthermia"[All Fields] OR "hyperthermias"[All Fields]) AND ("seizure"[All Fields] OR "seizures"[All Fields] OR "convulsion"[All Fields] OR convulsions)))

EMBASE (491 results):
(('febrile seizure'/exp OR 'febrile convulsion'/exp) OR (('fever'/exp OR 'fever' OR 'fevers' OR 'febrile' OR 'pyrexia' OR 'pyrexial' OR 'pyrexias' OR 'hyperthermia'/de OR 'hyperthermia' OR 'hyperthermias') AND ('seizure' OR 'seizures' OR 'convulsion' OR 'convulsions')))

Scopus (473 results):
(TITLE-ABS-KEY ("febrile" OR "fever" OR "fevers" OR "pyrexia" OR "pyrexial" OR "pyrexias" OR "hyperthermia" OR "hyperthermias") AND TITLE-ABS-KEY ("seizure" OR "seizures" OR "convulsion" OR "convulsions"))

Fever (no seizures)

PubMed (1098 results):
("fever"[MeSH Terms] OR "fever"[All Fields] OR "fevers"[All Fields] OR "febrile"[All Fields] OR "pyrexia"[All Fields] OR "pyrexial"[All Fields] OR "pyrexias"[All Fields] OR "hyperthermia"[All Fields] OR "hyperthermias"[All Fields]) NOT ("seizure"[All Fields] OR "seizures"[All Fields] OR "convulsion"[All Fields] OR convulsions OR "seizures, febrile"[MeSH Terms])

EMBASE (4418 results):
('fever'/exp OR 'fever' OR 'fevers' OR 'febrile' OR 'pyrexia' OR 'pyrexial' OR 'pyrexias' OR 'hyperthermia'/de OR 'hyperthermia' OR 'hyperthermias') NOT ('seizure' OR 'seizures' OR 'convulsion' OR 'convulsions' OR 'febrile seizure'/exp OR 'febrile convulsion'/exp)

Seizures (no fever)

PubMed (54 results):
("seizure"[All Fields] OR "seizures"[All Fields] OR "convulsion"[All Fields] OR convulsions) NOT ("fever"[MeSH Terms] OR "fever"[All Fields] OR "fevers"[All Fields] OR "febrile"[All Fields] OR "pyrexia"[All Fields] OR "pyrexial"[All Fields] OR "pyrexias"[All Fields] OR "hyperthermia"[All Fields] OR "hyperthermias"[All Fields] OR "seizures, febrile"[MeSH Terms])

EMBASE (258 results):
('seizure' OR 'seizures' OR 'convulsion' OR 'convulsions') NOT ('fever'/exp OR 'fever' OR 'fevers' OR 'febrile' OR 'pyrexia' OR 'pyrexial' OR 'pyrexias' OR 'hyperthermia'/de OR 'hyperthermia' OR 'hyperthermias' OR 'febrile seizure'/exp OR 'febrile convulsion'/exp)

Hypersensitivity

PubMed (V2 1115 results):
"anaphylaxis"[MeSH Terms] OR "anaphylaxis"[All Fields] OR "anaphylactic"[All Fields] OR "angioedema"[MeSH Terms] OR "angioedema"[All Fields] OR (("quincke"[All Fields] OR "quinckes"[All Fields] OR "quincke's"[All Fields] OR "angioneurotic"[All Fields] OR "facial"[All Fields]) AND ("edema"[MeSH Terms] OR "edema"[All Fields] OR "oedema"[All Fields])) OR "hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "hypersensitivities"[All Fields] OR "allergy"[All Fields] OR "allergy and immunology"[MeSH Terms] OR "allergies"[All Fields] OR "allergic"[All Fields] OR "pruritus"[MeSH Terms] OR "pruritus"[All Fields] OR "itching"[All Fields] OR "Stevens-Johnson Syndrome"[All Fields] OR "Stevens Johnson Syndrome"[All Fields] OR "toxic epidermal necrolysis"[All Fields] OR "toxic epidermal necrolyses"[All Fields] OR "nonstaphylococcal scalded skin syndrome"[All Fields] OR "Lyell syndrome"[All Fields] OR "Lyell's syndrome"[All Fields] OR "Lyells syndrome"[All Fields] OR "Lyell syndromes"[All Fields] OR "Lyell's syndromes"[All Fields] OR "Lyells syndromes"[All Fields] OR "urticaria"[MeSH Terms] OR urticaria[All Fields] OR urticarias[All Fields] OR hives[All Fields] OR "vasculitis"[MeSH Terms] OR vasculitis[All Fields] OR vasculitides[All Fields] OR angiitis[All Fields] OR angiitides[All Fields]

EMBASE (V2 1249 results):
'anaphylaxis'/de OR anaphylaxis:ti OR 'anaphylactic shock'/de OR 'anaphylactic shock':ti OR 'angioedema'/de OR angioedema:ti OR angioedemas:ti OR 'quincke edema'/de OR 'quincke edema':ti OR 'quinckes edema':ti OR 'quincke oedema':ti OR 'quincke edema':ti OR 'giant urticaria'/de OR 'giant urticaria':ti OR 'angioneurotic edema'/de OR 'angioneurotic edema':ti OR 'facial edema'/de OR 'facial edema':ti OR 'facial oedema':ti OR 'hypersensitivity'/de OR hypersensitivity:ti OR hypersensitivities:ti OR 'allergy'/de OR allergy:ti OR allergies:ti OR 'allergic reaction':ti OR 'allergic reactions':ti OR 'allergic conjunctivitis'/de OR 'allergic conjunctivitis':ti OR 'respiratory hypersensitivity':ti OR 'respiratory hypersensitivities':ti OR 'immediate hypersensitivity'/de OR 'immediate hypersensitivity':ti OR 'immediate hypersensitivities':ti OR 'pruritus'/de OR pruritus:ti OR itching:ti OR 'stevens johnson syndrome'/de OR 'stevens johnson syndrome':ti OR 'stevens-johnson syndrome':ti OR 'toxic epidermal necrolysis'/de OR 'toxic epidermal necrolysis':ti OR 'toxic epidermal necrolyses':ti OR 'nonstaphylococcal scalded skin syndrome':ti OR 'lyell syndrome':ti OR 'lyell syndromes':ti OR 'lyells syndrome':ti OR 'lyells syndromes':ti OR urticaria:ti OR urticarias:ti OR hives:ti OR vasculitis:ti OR vaculitides:ti OR angiitis:ti OR angiitides:ti OR anaphylaxis:ab OR 'anaphylactic shock':ab OR angioedema:ab OR angioedemas:ab OR 'quincke edema':ab OR 'quinckes edema':ab OR 'quincke oedema':ab OR 'quincke edema':ab OR 'giant urticaria':ab OR 'angioneurotic edema':ab OR 'facial edema':ab OR 'facial oedema':ab OR hypersensitivity:ab OR hypersensitivities:ab OR allergy:ab OR allergies:ab OR 'allergic reaction':ab OR 'allergic reactions':ab OR 'allergic conjunctivitis':ab OR 'respiratory hypersensitivity':ab OR 'respiratory hypersensitivities':ab OR 'immediate hypersensitivity':ab OR 'immediate hypersensitivities':ab OR pruritus:ab OR itching:ab OR 'stevens johnson syndrome':ab OR 'stevens-johnson syndrome':ab OR 'toxic epidermal necrolysis':ab OR 'toxic epidermal necrolyses':ab OR 'nonstaphylococcal scalded skin syndrome':ab OR 'lyell syndrome':ab OR 'lyell syndromes':ab OR 'lyells syndrome':ab OR 'lyells syndromes':ab OR urticaria:ab OR urticarias:ab OR hives:ab OR vasculitis:ab OR vaculitides:ab OR angiitis:ab OR angiitides:ab

Bells Palsy

PubMed (36 results):
"Bell Palsy"[MeSH] OR ("Bell Palsy"[All Fields] OR "Bells Palsy"[All Fields] OR "Bell's Palsy"[All Fields] OR "Bell Palsies"[All Fields] OR "Bells Palsies"[All Fields] OR "Bell's Palsies"[All Fields]) OR ("facial neuropathy"[All Fields] OR "facial paralysis"[All Fields] OR "facial paralyses"[All Fields] OR "facial palsy"[All Fields] OR "facial palsies"[All Fields])

EMBASE (191 results):
'bell palsy'/exp OR ('Bell Palsy' OR 'Bells Palsy' OR 'Bell Palsies' OR 'Bells Palsies') OR ('facial neuropathy' OR 'facial paralysis' OR 'facial paralyses' OR 'facial palsy' OR 'facial palsies')

MS

PubMed (83 results):
("multiple sclerosis"[MeSH Terms] OR "multiple sclerosis"[All Fields] OR "disseminated sclerosis"[All Fields] OR "insular sclerosis"[All Fields])

EMBASE (397 results):
('multiple sclerosis'/exp OR 'disseminated sclerosis' OR 'insular sclerosis')

Encephalomyelitis, Acute Disseminated

PubMed (56 results):
"encephalomyelitis, acute disseminated"[MeSH Terms] OR (("acute disseminated"[All Fields] OR "postinfectious" OR "post-infectious" OR "post infectious" OR "postinfection" OR "post-infection" OR "post infection" OR "postvaccinalis" OR "postvaccination" OR "postvaccine" OR "post-vaccinal"[All Fields] OR "post vaccinal"[All Fields] OR "postvaccinal"[All Fields] OR "post-vaccinial"[All Fields] OR "post vaccinial"[All Fields] OR "postvaccinial"[All Fields]) AND ("encephalitis"[All Fields] OR "encephalitides"[All Fields] OR "encephalomyelitis"[All Fields] OR "encephalomyelitides"[All Fields])) OR "vaccination encephalitis"[All Fields]

EMBASE (154 results):
'acute disseminated encephalomyelitis'/exp OR ('acute disseminated' OR 'postinfectious' OR 'post-infectious' OR 'postinfection' OR 'post-infection' OR 'postvaccinalis' OR 'postvaccinal' OR 'post-vaccinal' OR 'postvaccinial' OR 'post-vaccinial' OR 'postvaccination' OR 'postvaccine' AND (encephalitis OR encephalitides OR encephalomyelitis OR encephalomyelitides)) OR 'vaccination encephalitis'

LAIV and Asthma/Wheezing

PubMed (70 results):
"LAIV"[All Fields] OR "live attenuated"[All Fields] OR "FluMist"[All Fields] OR "Fluenz"[All Fields] OR "CAIV-T"[All Fields] OR "cold adapted"[All Fields] OR "cold-adapted"[All Fields] OR "nasal spray"[All Fields] OR "pLAIV"[All Fields]

AND

"asthma"[Mesh] or "asthma"[All Fields] or "asthmatic"[All Fields] or "lung allergy"[All Fields] or "wheezing"[All Fields] or "wheeze"[All Fields] or "wheezes"[All Fields] or "wheezed"[All Fields] or "rhonchi"[All Fields] or "rhonchus"[All Fields] or "rale"[All Fields] or "rales"[All Fields] or "Bronchiolitis"[Mesh] or "Bronchiolitis"[All Fields] or "cough"[Mesh] or "cough"[All Fields] or "coughs"[All Fields] or "coughing"[All Fields] or "coughed"[All Fields] or "respiratory sounds"[Mesh] or "abnormal respiratory sounds"[All Fields]

EMBASE (245 results):
'LAIV' OR 'live attenuated' OR 'FluMist' OR 'Fluenz' OR 'CAIV-T' OR 'cold-adapted' OR 'nasal spray' OR 'pLAIV'

AND

'asthma'/exp or 'asthma' or 'asthmatic' or 'lung allergy' or 'wheezing'/exp or 'wheezing' or 'wheeze' or 'wheezes' or 'wheezed' or 'rhonchi' or 'rhonchus' or 'rale' or 'rales' or 'Bronchiolitis'/exp or 'Bronchiolitis' or 'cough'/de or 'cough' or 'coughs' or 'coughed' or 'coughing' or 'abnormal respiratory sound'/exp or 'abnormal respiratory sound'

Narcolepsy

PubMed (84 results):
"Narcolepsy"[Mesh] OR "Cataplexy"[Mesh] OR "Paroxysmal Sleep"[All Fields] OR "Narcoleptic"[All Fields] OR "Gelineau"[All Fields] OR "Gelineau's"[All Fields] OR "Gelineaus"[All Fields] OR "Narcolepsy"[All Fields] OR "Cataplexy"[All Fields] OR "Narcolepsy-Cataplexy"[All Fields] OR "sleep epilepsy"[All Fields] OR "narcolepsis"[All Fields] OR "neurolepsy"[All Fields]

EMBASE (200 results):
'narcolepsy'/exp OR 'cataplexy'/exp OR 'Paroxysmal Sleep' OR 'Narcoleptic' OR 'Gelineau' OR 'Gelineaus' OR 'Narcolepsy' OR 'Cataplexy' OR 'Narcolepsy-Cataplexy' OR 'sleep epilepsy' OR 'narcolepsis' OR 'neurolepsy'

Pericarditis

PubMed (12 results):
"Pericarditis"[Mesh] OR "Pericarditis, Constrictive"[Mesh] OR "Pericarditis"[All Fields] OR "Pericarditides"[All Fields] OR "Pericardial"[All Fields] OR "Pericardium"[All Fields] OR "Pick Disease of Heart"[All Fields] OR "Pick's Disease of Heart"[All Fields] OR "Picks Disease of Heart"[All Fields] OR "Heart Pick Disease"[All Fields] OR "Heart Pick's Disease"[All Fields] OR "Heart Picks Disease"[All Fields]

EMBASE (113 results):
'pericarditis'/de OR 'constrictive pericarditis'/de OR 'Pericarditis' OR 'Pericarditides' OR 'Pericardial' OR 'Pericardium' OR 'Pick Disease of Heart' OR 'Picks Disease of Heart' OR 'Heart Pick Disease' OR 'Heart Picks Disease'

Brachial Neuritis, neuralgia, paresthesia

PubMed (V2 103 results):
"Brachial Plexus Neuritis"[Mesh] OR "Neuralgia"[Mesh] OR "Paresthesia"[Mesh] OR "neuritis" OR "neuritides" OR "neuralgia" OR "neuralgias" OR "neuralgic" OR "neuropathy" OR "neuropathic" OR "nerve pain" OR "nerve pains" OR "paresthesia" OR "paresthesias" OR "dysesthesia" OR "dysesthesias" OR "formication" OR "formications" OR "Parsonage Aldren Turner Syndrome" OR "Parsonage-Aldren-Turner Syndrome" OR "Parsonage Turner Syndrome" OR "Parsonage-Turner Syndrome"

EMBASE (V2 234 results):
'brachial plexus neuropathy'/de OR 'brachialgia'/de OR 'neuralgia'/de OR 'paresthesia'/de OR 'injection site paresthesia'/de OR 'neuritis':ti OR 'neuritides':ti OR 'neuralgia':ti OR 'neuralgias':ti OR 'neuralgic':ti OR 'neuropathy':ti OR 'neuropathic':ti OR 'nerve pain':ti OR 'nerve pains':ti OR 'paresthesia':ti OR 'paresthesias':ti OR 'dysesthesia':ti OR 'dysesthesias':ti OR 'formication':ti OR 'formications':ti OR 'Parsonage Aldren Turner Syndrome':ti OR 'Parsonage Turner Syndrome':ti OR 'neuritis':ab OR 'neuritides':ab OR 'neuralgia':ab OR 'neuralgias':ab OR 'neuralgic':ab OR 'neuropathy':ab OR 'neuropathic':ab OR 'nerve pain':ab OR 'nerve pains':ab OR 'paresthesia':ab OR 'paresthesias':ab OR 'dysesthesia':ab OR 'dysesthesias':ab OR 'formication':ab OR 'formications':ab OR 'Parsonage Aldren Turner Syndrome':ab OR 'Parsonage Turner Syndrome':ab

Bursitis

PubMed (31 results):
"Bursitis"[Mesh] OR "Bursitis"[All Fields] OR "Bursitides"[All Fields] OR "Adhesive Capsulitis"[All Fields] OR "Adhesive Capsulitides"[All Fields] OR "Shoulder Impingement Syndrome"[Mesh] OR "Shoulder Impingement Syndrome"[All Fields] OR (("periarthritis"[Mesh] OR "periarthritis"[All Fields] OR "tenosynovitus"[All Fields]) AND ("shoulder"[All Fields] OR "humeroscapular"[All Fields] OR "humeroscapularis"[All Fields] OR "scapulohumeral"[All Fields] OR "scapulohumeralis"[All Fields] OR "scapulo"[All Fields] OR "scapularis"[All Fields])) OR "UAIRVA"[All Fields] OR "deltoid"[All Fields] OR "frozen shoulder"[All Fields] OR "shoulder pain"[All Fields] OR "shoulder injury"[All Fields] OR "shoulder dysfunction"[All Fields] OR "shoulder stiffness"[All Fields] OR "stiff shoulder"[All Fields] OR "rigid shoulder"[All Fields] OR "shoulder rigidity"[All Fields] OR "arm pain"[All Fields] OR "arm dysfunction"[All Fields] OR "Arm Injuries"[Mesh] OR "arm injury"[All Fields] OR "arm injuries"[All Fields]

EMBASE (56 results):
'bursitis'/exp or 'bursitides' or 'adhesive capsulitis' or 'adhesive capsulitides' or 'shoulder impingement syndrome'/exp or 'humeroscapular periarthritis'/exp or 'UAIRVA' or 'deltoid muscle'/exp or 'frozen shoulder'/exp or 'shoulder pain'/exp or 'shoulder injury'/exp or 'shoulder dysfunction' or 'shoulder stiffness' or 'stiff shoulder' or 'rigid shoulder' or 'shoulder rigidity' or 'arm pain'/exp or 'arm dysfunction'

Encephalopathy, Encephalomyopathy, Encephalitis

PubMed (V2 236 results):
"encephalopathy"[All Fields] OR "encephalon"[All Fields] OR ("Intracranial"[All Fields] AND ("central nervous system"[All Fields] OR "CNS"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "disorder"[All Fields] OR "diseases"[All Fields] OR "disorders"[All Fields])) OR "encephalopathia"[All Fields] OR "panencephalopathy"[All Fields] OR "leigh disease"[Mesh] OR "leigh disease"[All Fields] OR "leigh's disease"[All Fields] OR "leighs disease"[All Fields] OR "leigh syndrome"[All Fields] OR "encephalomyopathy"[All Fields] OR "encephalomyopathies"[All Fields] OR "encephalitis"[MeSH Terms] OR "encephalitis"[All Fields] OR "encephalitides"[All Fields] OR "brain inflammation"[All Fields] OR "cerebritis"[All Fields] OR "encephalitis"[All Fields]

EMBASE (V2 305 results):
'encephalopathy':ti OR 'encephalon':ti OR 'intracranial central nervous system disorder':ti OR 'intracranial central nervous system disorders':ti OR 'intracranial cns disorder':ti OR 'intracranial cns disorders':ti OR 'encephalopathia':ti OR 'panencephalopathy':ti OR 'leigh disease'/de OR 'leigh disease':ti OR 'leighs disease':ti OR 'leigh syndrome':ti OR 'encephalomyopathy'/de OR 'encephalomyopathy':ti OR 'encephalomyopathies':ti OR 'encephalitis'/de OR 'encephalitis':ti OR 'encephalitides':ti OR 'brain inflammation':ti OR 'cerebritis':ti OR 'enkephalitis':ti OR 'encephalopathy':ab OR 'encephalon':ab OR 'intracranial central nervous system disorder':ab OR 'intracranial central nervous system disorders':ab OR 'intracranial cns disorder':ab OR 'intracranial cns disorders':ab OR 'encephalopathia':ab OR 'panencephalopathy':ab OR 'leigh disease':ab OR 'leighs disease':ab OR 'leigh syndrome':ab OR 'encephalomyopathy':ab OR 'encephalomyopathies':ab OR 'encephalitis':ab OR 'encephalitides':ab OR 'brain inflammation':ab OR 'cerebritis':ab OR 'enkephalitis':ab

Myelitis

PubMed (32 results):
"Myelitis, Transverse"[Mesh] OR "Myelitis"[All Fields] OR "Myelitides"[All Fields] OR "Myelopathy"[All Fields] OR "Myelopathies"[All Fields] OR "Spinal Cord Inflammation"[All Fields] OR "Spinal Cord Inflammations"[All Fields] OR "Spinal Inflammation"[All Fields] OR "Spinal Inflammations"[All Fields]

EMBASE (136 results):
'myelitis'/de or 'myelitis' or 'myelitides' or 'myelopathy' or 'myelopathies' or 'spinal cord inflammation' or 'spinal cord inflammations' or 'spinal inflammation' or 'spinal inflammations'

ITP, Transient thrombocytopenia, purpura

PubMed (V2 65 results):
"Purpura, Thrombocytopenic, Idiopathic"[Mesh] OR "Thrombocytopenia"[Mesh] OR "Purpura"[Mesh] OR "ITP"[All Fields] OR "Werlhof's Disease"[All Fields] OR "Werlhofs Disease"[All Fields] OR "Werlhof Disease"[All Fields] OR "morbus werlhof"[All Fields] OR "thrombocytopenic"[All Fields] OR "thrombocytopenia"[All Fields] OR "thrombocytopenias"[All Fields] OR "thrombopenia"[All Fields] OR "thrombopenias"[All Fields] OR "macrothrombocytopenia"[All Fields] OR "macrothrombocytopenias"[All Fields] OR "platelet deficiency"[All Fields] OR "platelet deficiencies"[All Fields] OR "thrombocyte deficiency"[All Fields] OR "thrombocyte deficiencies"[All Fields] OR "thrombopenia"[All Fields] OR "thrombopenias"[All Fields] OR "purpura"[All Fields] OR "purpuras"[All Fields] OR "petechiae"[All Fields]

EMBASE (V2 339 results):
'idiopathic thrombocytopenic purpura'/de or 'thrombocytopenia'/de or 'purpura'/de or 'ITP' or 'Werlhofs Disease' or 'Werlhof Disease' or 'morbus werlhof' or 'thrombocytopenic' or 'thrombocytopenia' or 'thrombocytopenias' or 'thrombopenia' or 'thrombopenias' or 'macrothrombocytopenia' or 'macrothrombocytopenias' or 'platelet deficiency' or 'platelet deficiencies' or 'thrombocyte deficiency' or 'thrombocyte deficiencies' or 'thrombopenia' or 'thrombopenias' or 'purpura' or 'purpuras' or 'petechiae'

Arthritis

PubMed (V2 158 results):
"Arthritis"[Mesh] OR "Arthritis"[All Fields] OR "Arthritides"[All Fields] OR "Polyarthritis"[All Fields] OR "Polyarthritides"[All Fields] OR "arthrochondritis"[All Fields] OR "arthrosynovitis"[All Fields] OR "joint inflammation"[All Fields] OR "joint inflammations"[All Fields] OR "oligoarthritis"[All Fields]

EMBASE (V2 356 results):
'arthritis'/de OR 'arthritis':ti OR 'arthritides':ti OR 'polyarthritis':ti OR 'polyarthritides':ti OR 'arthrochondritis':ti OR 'arthrosynovitis':ti OR 'joint inflammation':ti OR 'joint inflammations':ti OR 'oligoarthritis':ti OR 'arthritis':ab OR 'arthritides':ab OR 'polyarthritis':ab OR 'polyarthritides':ab OR 'arthrochondritis':ab OR 'arthrosynovitis':ab OR 'joint inflammation':ab OR 'joint inflammations':ab OR 'oligoarthritis':ab

DVT/VTE

PubMed (11 results):
"Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh] OR "Venous Thromboembolism"[All Fields] OR "Vein Thromboembolism"[All Fields] OR "Venous Thrombosis"[All Fields] OR "Venous Thromboses"[All Fields] OR "Deep Vein Thrombosis"[All Fields] OR "Deep Vein Thromboses"[All Fields] OR "Deep-Vein Thrombosis"[All Fields] OR "Deep-Vein Thromboses"[All Fields] OR "deep thrombophlebitis"[All Fields] OR "deep venous thrombus"[All Fields] OR "Phlebothrombosis"[All Fields] OR "Phlebothromboses"[All Fields]

EMBASE (163 results):
'venous thromboembolism'/exp or 'deep vein thrombosis'/exp or 'Venous Thromboembolism' or 'Vein Thromboembolism' or 'Venous Thrombosis' or 'Venous Thromboses' or 'Deep Vein Thrombosis' or 'Deep Vein Thromboses' or 'Deep-Vein Thrombosis' or 'Deep-Vein Thromboses or 'deep thrombophlebitis' or 'deep venous thrombus' or 'Phlebothrombosis' or 'Phlebothromboses'

Myalgia/Malaise

PubMed (130 results):
"Myalgia"[Mesh] OR "myalgia"[All Fields] OR "muscle pain"[All Fields] OR "muscle pains"[All Fields] OR "muscle soreness"[All Fields] OR "muscle sorenesses"[All Fields] OR "muscle tenderness"[All Fields] OR "myodynia"[All Fields] OR "malaise"[All Fields]

EMBASE (1703 results):
'myalgia'/de or 'malaise'/exp or 'myalgia' or 'muscle pain' or 'muscle pains' or 'muscle soreness' or 'muscle sorenesses' or 'muscle tenderness' or 'myodynia' or 'malaise'

Cellulitis, Large Injection Site Swelling/Induration

PubMed (24 results):
"Cellulitis"[Mesh] OR "Cellulitis"[All Fields] OR "Phlegmon"[All Fields] OR "Large injection site swelling"[All Fields] OR "Large injection site induration"[All Fields] OR "Large injection site reaction"[All Fields] OR "Large injection site reactions"[All Fields] OR "Large injection site inflammation"[All Fields] OR "Large injection site inflammations"[All Fields] OR "Large injection-site swelling"[All Fields] OR "Large injection-site induration"[All Fields] OR "Large injection-site reaction"[All Fields] OR "Large injection-site reactions"[All Fields] OR "Large injection-site inflammation"[All Fields] OR "Large injection-site inflammations"[All Fields] OR "Large vaccination site swelling"[All Fields] OR ""Large vaccination site induration"[All Fields] OR "Large vaccination site reaction"[All Fields] OR "Large vaccination site reactions"[All Fields] OR "Large vaccination site inflammation"[All Fields] OR ""Large vaccination site inflammations"[All Fields] OR "Large vaccination-site swelling"[All Fields] OR ""Large vaccination-site induration"[All Fields] OR "Large vaccination-site reaction"[All Fields] OR ""Large vaccination-site reactions"[All Fields] OR "Large vaccination-site inflammation"[All Fields] OR "Large vaccination-site inflammations"[All Fields] OR "extensive swelling"[All Fields] OR "extensive induration"[All Fields] OR "extensive reaction"[All Fields] OR "extensive reactions"[All Fields] OR "extensive inflammation"[All Fields] OR ""extensive inflammations"

EMBASE (700 results):
'cellulitis'/exp or 'injection site swelling'/exp or 'injection site induration'/exp or 'injection site inflammation'/exp or 'injection site cellulitis'/exp or 'Cellulitis' or 'Phlegmon' or 'Large injection' or 'site swelling' or 'Large injection site induration' or 'Large injection site reaction' or 'Large injection site reactions' or 'Large injection site inflammation' or 'Large injection site inflammations' or 'Large injection-site swelling' or 'Large injection-site induration' or 'Large injection-site reaction' or 'Large injection-site reactions' or 'Large injection-site inflammation' or 'Large injection-site inflammations' or 'Large vaccination site swelling' or 'Large vaccination site induration' or 'Large vaccination site reaction' or 'Large vaccination site reactions' or 'Large vaccination site inflammation' or 'Large vaccination site inflammations' or 'Large vaccination-site swelling' or 'Large vaccination-site induration' or 'Large vaccination-site reaction' or 'Large vaccination-site reactions' or 'Large vaccination-site inflammation' or 'Large vaccination-site inflammations' or 'extensive swelling' or 'extensive induration' or 'extensive reaction' or 'extensive reactions' or 'extensive inflammation' or 'extensive inflammations'

Willidentifiedafety data.

Appendix 2. Results of literature Searches by article type

Articles screened													
Database search[c]		Excluded				Article types reviewed[b]					Final		
Adverse event	Initial search result total	Not in English	Comments/Letters/ Notes/Editorials/ News	Not in humans[a]	Not in children[a]	Reviews	Case reports and series	Conference materials	Clinical trials[a]	Other	Data used in table	Otherwise helpful	Total included
GBS	1940	173	289	N/A	N/A	272	56	70	N/A	286	24	32	56
Febrile seizures	1058	50	95	N/A	N/A	193	18	35	N/A	208	40	50	90
Fever (no seizures)	5497	547	281	499	3101	116	47	42	254	409			
Seizures (no fever)	312	20	17	17	N/A	86	20	18	N/A	107			
Hypersensitivity	2364	264	172	298	1097	86	19	29	91	238			
MS	480	30	44	N/A	N/A	179	8	51	N/A	109	15	19	34
Bells Palsy	227	18	16	N/A	N/A	76	12	20	N/A	63			16
ADEM	210	33	11	N/A	N/A	46	24	15	N/A	49			56
LAIV and Asthma/Wheezing	315	9	16	23	N/A	79	1	13	70	47			
Narcolepsy	284	40	62	N/A	N/A	38	12	37	N/A	49	15	39	54
Pericarditis	125	17	7	N/A	N/A	53	7	4	N/A	29			7
Brachial Neuritis/ Neuralgia/Paresthesia	337	29	27	33	N/A	50	49	23	15	60			
Bursitis	87	3	6	5	N/A	16	15	2	13	15			
Encephalopathy/ Encephalomyopathy/ Encephalitis	541	109	14	66	N/A	113	30	20	11	132			
Myelitis	168	16	12	8	N/A	45	17	11	6	37			
ITP/Transient Thrombocytopenia/Purpura	404	45	30	16	N/A	135	38	19	17	74	8	12	20
Arthritis	514	22	47	32	N/A	104	20	65	34	111			45
DVT/VTE	174	15	12	N/A	N/A	75	7	14	15	28			
Cellulitis/Large Injection Site Swelling	724	13	18	16	N/A	185	13	12	268	188			20
Syncope	117	3	4	2	N/A	38	3	8	13	46			
General Safety Data – Inactivated Influenza Vaccines	15,878					1985	416	508	807	2285			87
General Safety Data – LAIV										6001			99

[a] Only some Adverse Events were screened for this category.

[b] Articles remaining after primary exclusion steps were extracted to EndNote by publication or study type and duplicates were deleted; numbers here represent final numbers after deletion of duplicates.

[c] PubMed and EMBASE for all Adverse Events, Scopus as well for GBS and Febrile Seizures.

Appendix 3. Recently Produced Influenza Vaccines

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Abbott	UK	Imuvac	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A) B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B)	Inactivated	Eggs	6 mos+
Abbott	Netherlands	Influvac Desu	2013–14	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A) B/Massachusetts/2/2012-derived strain used (NYMC BX-51B)	Inactivated	Eggs	6 mos+
Abbott	UK	Influvac sub-unit	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A) B/Massachusetts/2/2012-derived strain used (NYMC BX-51B)	Inactivated	Eggs	6 mos+
Adimmune	Taiwan		2009–10	Pandemic	A/California/07/2009	Inactivated	Eggs	
Adimmune	Taiwan	AdimFlu-S (Pediatric Use) Alt link	2013–14 northern hemisphere	Seasonal	A/California/7/2009 (H1N1) like virus A/California/7/2009 (Reassortant NYMC X-179A) (H1N1) A(H3N2) virus antigenically like the cell-propogated prototype virus A/Victoria/361/2011 A/Texas/50/2012 (Reassortant NYMC X-223) (H3N2) B/Massachusetts/2/2012 like virus B/Massachusetts/2/2012 (Reassortant NYMC BX-51B)	Inactivated	Eggs	6 mos – <3 yrs
Baxter	Austria	Celvapan		Pandemic	A/California/07/2009 (H1N1)v	Inactivated	Vero cells	6 mos+
Baxter	Austria	Pandemic Influenza Vaccine H5N1 Baxter		Pandemic	A/Vietnam/1203/2004 (H5N1)	Inactivated	Vero cells	6 mos+
Baxter	Czech Republic/ Austria	Vepacel		Pandemic	A/Vietnam/1203/2004 (H5N1)	Inactivated	Vero cells	6 mos+
Berna Biotech	Switzerland	Inflexal®V	2007–8	Seasonal	A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 (B)	Inactivated	Eggs	
Berna Biotech – Crucell – Solvay	Switzerland/ Netherlands		2000	Pandemic	A/Hong Kong/1073/99 (H9N2)	Inactivated	Eggs	

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Bharat Biotech	India	HNVAC		Pandemic	A/CALIFORNIA/7/2009 NYMC X-179-A obtained from WHO-accredited Centers for Disease Control and Prevention, USA	Inactivated	MDCK cells	18–65 yrs
Biken,	Japan		2006	Pandemic	A/Vietnam/1194/2004	Inactivated	Egg	
Biken,	Japan	Influenza HA Vaccine?	2010	Seasonal	A/California/7/2009 (H1N1) A/Victoria/210/2009 (H3N2) B/Brisbane/60/2008 (B)	Inactivated	Egg	
BioFarma,	Indonesia	Flubio Vaksin Influenza HA?	2010	Seasonal	A/Brisbane/59/2007 (H1N1) A(Uruguay/716/2007 (H3N2) B/Brisbane/60/2008 (b)	Inactivated	Egg	Older than 12 yrs?
Biondvax	Israel	M-001	2012	Seasonal	Epitopes of HA, NP and M1 from different strains of A and B subtypes (M-001)	Recombinant	*E. coli*	
Candia Healthcare	India		2010	Pandemic	A/California/07/2009	Inactivated	Eggs	
Cantacuzino Institute	Romania	Cantgrip™	2009–10	Pandemic	A/California/07/2009	Inactivated	Eggs	
Cantacuzino Institute	Romania	VACCIN GRIPAL TRIVALENT, PURIFICAT ŞI INACTIVAT	2011–12	Seasonal	A/California/7/2009 (H1N1) strain used: A/California/7/2009 (NYMC X-179A) A/Perth/16/2009 (H3N2) strain used: A/Victoria/210/2009 (NYMC X-187) B/Brisbane/60/2008 strain used: B/Brisbane/60/2008 (NYMC BX-35)	Inactivated	Eggs	36 mos+
Changchun Changsheng Life Sciences Ltd	China	Influenza Vaccine (split)	??	Seasonal	"A and B strain of influenza virus corresponding to prevailing epidemiological evidence of the year"	Inactivated	Chick embryo	6 mos+
Changzhou Yanshen Biotechnology Co., Ltd	China	Influenza						
Crucell	Netherlands		2009–10	Pandemic	A/Vietnam/1194/2004	Inactivated	Eggs	
Crucell	Netherlands	Inflexal V		Seasonal	Yearly WHO recommendations	Adjuvanted subunit	Eggs	6 mos+
CSL	US	Afluria	2014–15	Seasonal	A/California/7/2009 (H1N1), NYMC X-181, A/Texas/50/2012 (H3N2), NYMC X-223 B/Massachusetts/2/2012, NYMC BX-51B	Inactivated	Eggs	5–64 yrs
CSL	Australia	Fluvax	2014	Seasonal	A/California/7/2009 (NYMC X-181) (A/California/7/2009 (H1N1) – like) A/Texas/50/2012 (NYMC X-223) (A/Texas/50/2012 (H3N2) – like) B/Massachusetts/2/2012 (NYMC BX-51B) (B/Massachusetts/2/2012 – like)	Inactivated	Eggs	5 years + (caution for 5–9 yrs)
CSL	Australia	Panvax	2010	Pandemic	A/California/7/2009 (H1N1) (A/California/7/2009 (H1N1)v-like)	Inactivated	Eggs	18–65 yrs
Cytos	Switzerland		2013	Pandemic	Globulat head domain (gH1) of HA from A/California/07/2009	Virus-like particle based on RNA bacteriophage Qbeta (Leviviridae)	*E. coli*	

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Daiichi-Sankyo,	Japan		2010	Seasonal	A/California/7/2009 (H1N1) A/Victoria/210/2009 (H3N2) B/Brisbane/60/2008 (B)	Inactivated	Eggs	
Denka	Japan		2006	Pandemic	A/Vietnam/1194/2004	Inactivated	Eggs	
Denka Seiken,	Japan	Influenza Seiken HA?	2010–11	Seasonal	A/California/16/2009 (H1N1) A/Perch/210/2009 (H3N2) B/Brisbane/60/2008 (B)	Inactivated	Eggs	
Dynavax	?		2010	Pandemic	M2e and NP conjugated to oligonucelotide	Recombinant	No data	
Fort Ltd	Russia	Ultrix		Seasonal	A/New Caledonia/20/99 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	Inactivated		Ok for 6 yrs+ (earlier?)
Fraunhofer	US		2011	Pandemic	HAC1	Recombinant	*N. benthamiana* plant	
Green Cross Corporation	Korea	GC FLU inj (single dose vial)	2013–14	Seasonal	A/California/7/2009 reassortant virus NYMC X-181 (H1N1) A/Texas/50/2012 reassortant virus NYMC X-223A (H3N2) B/Massachusetts/02/2012 reassortant virus NYMC Bx-51B	Inactivated	Eggs	6 mos+
Green Cross Corporation	Korea	GC FLU Multi inj.	2013–14	Seasonal	A/California/7/2009 reassortant virus NYMC X-181 (H1N1) A/Texas/50/2012 reassortant virus NYMC X-223A (H3N2) B/Massachusetts/02/2012 reassortant virus NYMC Bx-51B	Inactivated	Eggs	6 mos+
Green Cross Corporation	Korea	Green Flu-S		Pandemic	A/California/7/2009 NYMC X-179A(H1N1)	Inactivated	Eggs	6 mos+
Green Hills Biotech	Austria		2007–08	Pandemic	A/New Caledonia/20/99-ΔNS1	Live attenuated	Vero cells	
Green Hills Biotech| Henogen	Austria| Belgium		2009	Pandemic	A/Vietnam/1203/2004-ΔNS1	Live attenuated	Vero cells	
GSK	Belgium	Adjupanrix	2014	Pandemic	A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14)	Inactivated	Eggs	18 yrs +
GSK	Germany	Arepanrix	2010	Pandemic	A/California/7/2009 (H1N1)v-like strain (X-179A)	Inactivated	Eggs	18 yrs +
GSK	UK	Fluarix	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain used (NIB-74xp) derived from A/Christchurch/16/2010 A/Texas/50/2012 (H3N2) derived strain used (NYMC X-233A) B/Massachusetts/02/2012 derived strain used (NYMC BX-51B)	Inactivated	Eggs	6 mos+
GSK	US	Fluarix Quadravalent	2014–15	Seasonal	A/Christchurch/16/2010 NIB-74XP (H1N1) (an A/California/7/2009-like virus), A/Texas/50/2012 NYMC X-223A (H3N2), B/Massachusetts/2/2012 NYMC BX-51B, B/Brisbane/60/2008	Inactivated	Eggs	3 yrs+

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
GSK	UK	Fluarix Tetra	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain used (NIB-74xp) derived from A/Christchurch/16/2010 A/Texas/50/2012 (H3N2) derived strains used (NYMC X-223A) B/Massachusetts/02/2012 derived strain used (NYMC BX-51B) (Yamagata lineage) B/Brisbane/60/2008 (Victoria lineage)	Inactivated	Eggs	3 yrs+
GSK	Canada	FluLaval	2013–14	seasonal	A/California/7/2009 (H1N1)-like strain: A/California/7/2009 X-179A A/Texas/50/2012 (H3N2)-like strain: A/Texas/50/2012 X-223A B/Massachusetts/2/2012-like strain: B/Massachusetts/2/2012 BX-51B	Inactivated	Eggs	18 yrs+
GSK	US	Flulaval Quadravalent	2014–15	Seasonal	A/California/7/2009 NYMC X-179A (H1N1), A/Texas/50/2012 NYMC X-223A (H3N2), B/Massachusetts/2/2012 NYMC BX-51B, B/Brisbane/60/2008	Inactivated	Eggs	3 yrs+
GSK	Canada	FluLaval Tetra	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-like virus A/Texas/50/2012 (H3N2)-like virus B/Massachusetts/2/2012-like virus B/Brisbane/60/2008-like virus	Inactivated	Eggs	
GSK	Belgium	Pandemrix		pandemic	A/California/7/2009 (H1N1)v-like strain (X-179A)	Inactivated	Eggs	6 mos+
GSK	Belgium	Prepandrix	2013-last reviewed	Pre-pandemic	A/Indonesia/05/2005 (H5N1) like strain used (PR8-IBCDC-RG2)	Inactivated	Eggs	18 yrs+
GSK	Belgium	Pumarix		pandemic	'A/Indonesia/05/2005 PR8-IBCDC-RG2' (H5N1)	Inactivated	Eggs	18 yrs+
Hokken, Saitama,	Japan		2005–06	Seasonal	A/New Caledonia/20/99 (H1N1) A/New York/55/04 (H3N2) B/hanghai/361/029 (B)	Inactivated	Eggs	
Hualan Biological	China		2009	Pandemic	A/California/07/2009	Inactivated	Eggs	
Hualan Biological	China	Influenza Vaccine (split virion)	2012	Seasonal	A/California/7/2009 (H1N1)pdm09-like virus A/Victoria/361/ 2011H3N2-like virus B/Wisconsin/1/2010-like virus	Inactivated	Eggs	3 yrs+
Immune Targeting Systems	UK		2010–11	Pandemic	Six fluorocarbon modified peptides that encapsulate multiple CD4+ and CD8+ T cell epitopes from nucleoprotein, matrix and polymerase 1 and 2 proteins	Peptide-based	None	

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Immunopreparat Research productive association	Russia	Influenza Vaccine						
Impfstoffwerk	Germany		2010–11	Pandemic	Modified Vaccinia virus Ankara (MVA) vector encoding NP and MI of strain A/Panama/2007/99	Recombinant	CEF	
Instituto Butantan	Brazil		2010	Pandemic	A/California/07/2009	Inactivated	Eggs	
Instituto Butantan	Brazil	CEPAS Also PI from IB	2014 (southern hemisphere)	Seasonal	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 B/Massachusetts/2/2012	Inactivated	Eggs (ovos)	6 mos+
Janssen-Cilag Ltd	UK	Viroflu	2013–14	Seasonal	A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-181) A/Victoria/361/2011 (H3N2)-like strain used (NYMC X-223) derived from A/Texas/50/2012 B/Massachusetts/2/2012-derived strain used (NYMC BX-51B)	Inactivated	Eggs	6 mos+
Kaketsuken	Japan		2006	Pandemic	A/Vietnam/1194/2004	Inactivated	Eggs	
Kaketsuken Biologicals	Japan	Influenza HA vaccine (in japanese)	2005	Seasonal	A/New Caledonia/20/99 (H1N1) A/New York/55/2004 (H3N2) B/Shanghai/361/2002 (B)	Inactivated	Eggs?	
Kitasato Institute	Japan		2006	Pandemic	A/Vietnam/1194/2004	Inactivated	Eggs	
Lanzhou Institute of Biological Products (LIBP)	China	Influenza						
LG Life Sciences	Korea		2004–5	Seasonal	A/New Caledonia/20/99 (H1N1) A/Fujian/411/2002 (H3N2) B/Shainghaia/361/2002 (B)	Inactivated	Eggs	
Liaoning Tiancheng Bio-pharmacy Insitute Co. Ltd	China	Influenza						
MedImmune	UK	FLUENZ nasal spray suspension	2013–14	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain A/Victoria/361/2011 (H3N2)-like strain B/Massachusetts/2/2012-like strain	Live attenuated	Eggs	24 mos–>18 yrs
MedImmune	UK	Fluenz Tetra nasal spray suspension	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-like strain A/Texas/50/2012 (H3N2)-like strain B/Brisbane/60/2008 (Victoria lineage)-like strain B/Massachusetts/2/2012 (Yamagata lineage)-like strain	Live attenuated	Eggs	24 mos–>18 yrs
MedImmune	USA	FluMist Quadrivalent	2014–15	Seasonal	A/California/7/2009 (H1N1) A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012 (B/Yamagata/16/88 lineage) B/Brisbane/60/2008 (B/Victoria/2/87 lineage)	Live attenuated	Eggs	2–49 yrs
MedImmune	USA	Influenza A (H1N1) 2009 monovalent vaccine nasal	2010	Pandemic	A/California/7/2009 (H1N1)v	Live	Eggs	2–49 yrs
Microgen	Russia		2009–10	Pandemic	A/California/07/2009	Live attenuated	Eggs	

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Microgen	Russia		2009–10	Pandemic	A/California/07/2009	Inactivated	Eggs	
Microgen	Russia	Grippol		Seasonal	changed yearly according to epidemic situation and WHO recommendations	Polymer-subunit		6 mos+
Microgen	Russia	INFLUENZA VIRUS VACCINE		Seasonal	changed yearly according to WHO recommendations	Live, Dry	Eggs	3 yrs+
Netherlands Vaccine Institute	Netherlands		2011	Pandemic	A/Uruguay/716/2007 (H3N2))	Inactivated	Eggs	
NIH|Novartis	USA|Italy		2009–10	Pandemic	A/California/07/2009	DNA Vaccine	*E. coli*	
NIH|Sanofi pasteur	USA		2011–12	Seasonal	2011–2012 seasonal strains	DNA Vaccine	DNA	
NIH|Sanofi pasteur	USA		2010–11	Pandemic	A/Indonesia/05/2005	DNA Vaccine	*E. coli*	
Nobilon International	Netherlands		2009	Seasonal	A/Brisbane/59/2007 (H1N1) A/Brisbane/10/2007 (H3N2) B/Florida/4/2006 (B)	Live attenuated	MDCK cells	
Novartis	Italy	Aflunov		Pre-pandemic	A/turkey/Turkey/1/05 (H5N1)-like strain (NIBRG-23)	Inactivated	Eggs	18 yrs+
Novartis	US	Agriflu	2013–14	Seasonal	A/California/7/2009, NYMC X-181 (H1N1) A/Texas/50/2012, NYMC X-223 (H3N2) B/Massachusetts/2/2012	Inactivated	Eggs	18 yrs+
Novartis	UK	Agrippal	2014–15 Season	Seasonal	A/California/7/2009 (H1N1)pdm09 – derived strain used (NYMC X-181 A/Texas/50/2012 (H3N2) – derived strain used (NYMC X-223) B/Massachusetts/2/2012 – (wild type)	Inactivated	Eggs	6 mos+
Novartis	Germany	Celtura	2010	Pandemic	A/California/7/2009 (H1N1)v-like strain used (X-179A)	Inactivated	MDCK	6 mos+
Novartis	Italy	Flucelvax	2014–15	Seasonal	A/Brisbane/10/2010 (H1N1) (an A/California/7/2009 -like virus); A/Texas/50/2012, NYMC X-223A (H3N2) B/Massachusetts/2/2012	Inactivated	MDCK	18 yrs+
Novartis	US	Flucelvax	2014–15	Seasonal	A/Brisbane/10/2010 (H1N1) (an A/California/7/2009-like virus) A/Texas/50/2012, NYMC X-223A (H3N2) B/Massachusetts/2/2012	Inactivated	Madin Darby Canine Kidney (MDCK)	18 yrs+
Novartis	UK	Fluvirin	2014–15	Seasonal	A/Christchurch/16/2010, NIB-74 (H1N1) (an A/California/7/2009-like virus); A/Texas/50/2012, NYMC X-223 (H3N2); B/Massachusetts/2/2012, NYMC BX-51B	Inactivated	Eggs	4 yrs
Novartis	UK	Fluvirin H1N1		Pandemic	A/California/7/2009 (H1N1)v-like virus	Inactivated	Eggs	4 yrs+
Novartis	Italy	Focetria		Pandemic	A/California/7/2009 (H1N1)v like strain (X-181)	Inactivated	Eggs	6 mos+
Novartis	Italy	Foclivia		Pandemic	A/Vietnam/1194/2004 (H5N1)	Inactivated	Eggs	18 yrs+
Novartis	Germany	Optaflu	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09 – like strain used A/Brisbane/10/2010 wild type A/Texas/50/2012 (H3N2) – derived strain used (NYMC X-223A) B/Massachusetts/2/2012	Inactivated	MDCK cells	18 yrs+

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Novartis	Italy	Prepandemic Influenza vaccine (H5N1)		Pre-pandemic	A/Vietnam/1194/2004 (H5N1)-like strain (NIBRG-14)	Inactivated	Eggs	18 yrs+
Novavax	US		2009	Pandemic	A/California/04/2009 (VLP consisting of HA, NA and M1)	Recombinant	Sf9 insect eggs	
Novavax	US		2005	Pandemic	A/chicken/Hong Kong/G9/97	Live attenuated	Eggs	
NTpharma LLC	Russia	AdeVac-Flu (intranasal)		Seasonal		Recombinant		
Omninvest,	Hungary	Fluval AB	2012–13	Seasonal	A/California/7/2009 (H1N1) origin, NYMC X-179A reassortant strain Victoria/361/2011 (H3N2) derived IVR-165 reassortant strain B/Wisconsin/1/2010-like B/Hubei-Wujiagang/158/2009	Inactivated	Eggs	3 yrs+
Omnivest	Hungary	Fluval P	2009	Pandemic	A/California/07/2009	Inactivated	Eggs	
Pax Vax	US		2011	Pandemic	A/Vietnam/1194/2004	Live Ad4-vectored vaccine	MRC5 cells	
Petrovax	Russia	Grippol Grippol Plus Grippol Neo	2008–09	seasonal	A/Brisbane/59/2007 (H1N1) -like virus; A/Brisbane/10/2007 (H3N2) -like virus; B/Florida/4/2006-like virus.	Inactivated	MDCK cells	6 mos+
Pfizer Limited	UK	Enzira	2014–15	Seasonal	A/California/7/2009 (H1N1) pdm09 – like strain (A/California/7/2009, NYMC X-181) A/Texas/50/2012 (H3N2) – like strain (A/Texas/50/2012, NYMC X-223) B/Massachusetts/2/2012 – like strain (B/Massachusetts/2/2012, NYMC BX-51B	Inactivated	Eggs	5 yrs+
Pharmaceutical Organization	Thailand		2012	Pandemic	A/California/07/2009	Live attenuated	Eggs	
PowderJect Vaccines	US		No data	Pandemic	A/Panama/2007/99 (H3N2)	DNA vaccine		
PowderMed	UK		2007	Seasonal	A/New Caledonia/20/99 (H1N1) A/Panama/2007/99 (H3N2) B/Jiangsu/10/2003()B)	DNA vaccine	*E. coli*	
Protein Sciences	US		2010–11	Pandemic	A/Indonesia/05/2005	Recombinant	SF9 insect cells	
Protein Sciences,	USA	Flublok	2014–15	Seasonal	A/California/7/2009 (H1N1) A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	Recombinant	Serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts	18–49 yrs
Research Foundation for Microb Dis of Osaka Univ	Japan		2009	Pandemic	A/California/07/2009	Inactivated	Eggs	
RIBSP	Khazakhstan		2010–11	Pandemic	A/California/07/2009	Inactivated	Eggs	
Sanofi Pasteur	US	Fluzone	2014–15	Seasonal	A/California/07/2009 X-179A (H1N1) A/Texas/50/2012 X-223A (H3N2) B/Massachusetts/02/2012 (B Yamagata lineage)	Inactivated	Eggs	6 mos+
Sanofi Pasteur	US	Fluzone High-Dose	2014–15	Seasonal	A/California/07/2009 X-179A (H1N1) A/Texas/50/2012 X-11 223A (H3N2 B/Massachusetts/02/2012 (B Yamagata lineage)	Inactivated	Eggs	65 yrs+

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Sanofi Pasteur	US	Fluzone Intradermal	2014–15	Seasonal	A/California/07/2009 X-179A (H1N1) A/Texas/50/2012 X-223A (H3N2) B/Massachusetts/02/2012 (B Yamagata lineage)	Inactivated	Eggs	18–64 yrs
Sanofi Pasteur	US	Fluzone single dose	2009–10	Seasonal	A/Brisbane/59/2007, IVR-148 (H1N1) A/Uruguay/716/2007, NYMC X-175C (an A/Brisbane/10/2007-like virus) (H3N2) B/Brisbane/60/2008	Inactivated	Eggs	6 mos+
Sanofi Pasteur	US	Fluzone® Quadrivalent	2014–15	Seasonal	A/California/07/2009 X-179A (H1N1) A/Texas/50/2012 X-223A (H3N2) (an A/Victoria/361/2011-like virus) B/Massachusetts/02/2012 (B Yamagata lineage) B/Brisbane/60/2008 (B Victoria lineage	Inactivated	Eggs	6 mos+
Sanofi Pasteur	France	IDflu	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-179A) A/Victoria/361/2011 (H3N2)-like strain used (NYMC X-223A) derived from/Texas/50/2012 B/Massachusetts/02/2012	Inactivated	Eggs	18–59 yrs
Sanofi Pasteur	UK	Inactivated Influenza Vaccine (Split Virion) BP	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-179A) A/Texas/50/2012 (H3N2)-derived strain used (NYMC X-223A) B/Massachusetts/2/2012	Inactivated	Eggs	6 mos+
Sanofi Pasteur	US	Influenza A (H1N1) 2009 monovalent vaccine – single dose vial		Pandemic	A/California/07/2009 (H1N1) v-like virus	Inactivated	Eggs	6 mos+
Sanofi Pasteur	US	Influenza A (H1N1) 2009 monovalent vaccine-multidose vial		Pandemic	A/California/07/2009 (H1N1) v-like virus	Inactivated	Eggs	6 mos+
Sanofi Pasteur	France	Intanza	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-179A A/Victoria/361/2011 (H3N2)-like strain used (NYMC X-223A) derived from A/Texas/50/2012 B/Massachusetts/02/2012	Inactivated	Eggs	18–59 yrs
Sanofi Pasteur	UK	INTANZA 9 micro-gram/strain suspension for injection	2014–15	seasonal	A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-179A) A/Texas/50/2012 (H3N2)-derived strain used (NYMC X-223A) B/Massachusetts/2/2012	Inactivated	Eggs	18–59 yrs
Sanofi Pasteur	France	Panenza		Pandemic	A/California/7/2009 (H1N1)v-like strain (NYMC X-179A)	Inactivated	Eggs	9 yrs+
Sanofi Pasteur	France	Vaxigrip	2010–11	Seasonal	A/California/7/2009 (H1N1) – derived strain used NYMC X-179A A/Perth/16/2009 (H3N2) – like strain used NYMC X-187 derived from A/Victoria/210/2009 B/Brisbane/60/2008	Inactivated	Eggs	6 mos+

Manufacturer	Manf Country	Vaccine	Date	Seasonal/ Pandemic	Strains	Type	Production Meth	Approved Ages
Sanofi Pasteur	New Zealand	Vaxigrip	Dated Jan 2013	Seasonal	A/California/7/2009 NYMC X-179A (A/California/7/2009 [H1N1]pdm09 – like), A/Victoria/361/2011 IVR-165 (A/Victoria/361/2011 [H3N2] – like), and B/Hubei-Wujiagang/158/2009 NYMC BX-39 (B/Wisconsin/1/2010 – like)	Inactivated	Eggs	6 mos+
Sanofi Pasteur	China	Vaxigrip (china)				Inactivated		6–35 mos
Sanofi Pasteur MSD Limited	UK	INTANZA 15 microgram/strain suspension for injection	2014–15	Seasonal	A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-179A) A/Texas/50/2012 (H3N2)-derived strain used (NYMC X-223A) B/Massachusetts/2/2012	Inactivated	Eggs	60 yrs+
SEEK	UK		2011	Pandemic	Unknown	Recombinant	Synthetic	
Serum Institute of India	India	NASOVAC – 5 dose vial		Pandemic	A/17/California/2009/38	Live Attenuated	Eggs	3 yrs+
Serum Institute of India	India	NASOVAC-S	2014 Southern Hemisphere	Seasonal	A(H1N1) Strain – A/17/California/2009/38 (H1N1) A(H3N2) Strain – A/17/Texas/2012/30 (H3N2) B Strain – B/60/Massachusetts/2012/10	Live Attenuated	Eggs	3 yrs+
Shanghai Institute of Biological Products (SIBP)	China		2009–10	Pandemic	A/California/07/2009	Inactivated	Eggs	
Sinovac Kexing Biological Product Co., Ltd	China	AnFlu™	2010	Seasonal	A/California/7/2009 A/Victoria/210/2009 B/Brisbane/60/2008	Inactivated	Chicken embryo	6 mos+
Sinovac Kexing Biological Product Co., Ltd	China	Panflu		Pandemic	A/Vietnam/1194/2004(H5N1)	Inactivated	Chicken embryo	18 yrs+
Sinovac Kexing Biological Product Co., Ltd	China	Panflu.1		Pandemic	H1N1	Inactivated	Chicken embryo	3 yrs+
Solvay Pharmaceuticals	Netherlands		2007–8	Seasonal	A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 (B)	Inactivated	Eggs	
Torlak Institute	Serbia and Montenegro	Vaccinum Influenzae		Seasonal		Inactivated	Eggs	
Vabiotech	Vietnam		2010–11	Pandemic	A/Vietnam/1194/2004	Inactivated	Primary monkey kidney cells	
Vaxinnate Corp	US		2009–10	Pandemic	HA globular head three formats of VAX128 (A, B, C)	Recombinant	*E. coli*	
Vical Incorp	US		2008	Pandemic	A/Vietnam/1203/2004 for H5; seasonal H1N1 or H3N2 for NP and M2	DNA vaccine		
Zhejiang Tianyuan - BioPharmaceutical Co. Ltd	China	Influenza				Inactivated		
Zydus	India?	Vaxiflu-S	2010	Pandemic	A/California/7/2009	Inactivated	Egg	18 yrs+

Appendix 4. Epidemiological Evidence for Association between Influenza Vaccines and Febrile Seizures by Year

Author Year Country	Influenza Season(s) & Age group	Study type	Vaccine type Dose	Number or proportion of febrile episodes (95% Confidence interval)	Number or proportion of febrile convulsions	Primary risk Estimate (95% Confidence interval)	Total time of Adverse Event Monitoring after vaccination	Time after vaccination AE noted
Marine 1976 England	1972 9mos-2Yrs	Clinical trial	Whole cell MIV 340 cca (IM) 500 cca (SC)	9/13 vaccinated	1/13 vaccinated	Not specified	24 hrs.	Fevers within 6-12 Hrs. Febrile seizure 7 Hrs.
Wright 1976 US	1973 1-6 Yrs.	Clinical trial	Whole cell MIV 250 cca[1] (0.25 mL)	12-28 mos 9/16 vaccinated 1/19 controls 3-6 Yrs. 2/29 vaccinated 0/4 controls	2/16 vaccinated 0/19 controls 0/29 vaccinated 0/4 controls	Not specified	24 hrs.	Fever 6-12 Hrs. Febrile seizure 6.5 Hrs.
Bernstein 1982 US	1978-1980 6-36 mos	Clinical trial	Whole cell Split 3.5 mg (0.25 mL)	Whole cell MIV 12/40 TIV 21/40 Split-virus MIV 6/37 TIV 0/37	0/77 vaccinated	Not specified	6-48 Hrs.	Not specified
Feldman 1985 US	Not specified 1-7 Yrs.	Randomized controlled trial	LAIV 0.5mL Whole cell MIV 8 μg (0.25 mL)	LAIV H1N1 0/29 LAIV H3N2 3/28 MIV H3N2 8/24 Placebo 0/30	LAIV H1N1 0/29 LAIV H3N2 0/28 MIV H3N2 1/24 Placebo 0/30	Not specified	LAIV 6 days MIV 6-12 hrs.	Most fevers within 24 Hrs. Febrile seizure within 6 days
France 2004 US	1993-1999 <18 Yrs.	Self-controlled case series	not specified	1,094/128,679 vaccinated	81/128,679 vaccinated	Not specified	Day 1-14	Febrile seizure within 14 days Control window: 15-28 days before and after vaccination
Nolan 2008 US, Australia	2000-2002 12-15 mos	Randomized controlled trial	LAIV 0.5 mL	MMR+Varicella+LAIV 417/422 LAIV 211/412	MMR+Varicella+LAIV 0/422 MMR+Varicella 0/411 LAIV 1/412	Not specified	41 days after concurrent vaccines and 10 days after LAIV	Time of Febrile seizure occurrence not specified

Author Year Country	Influenza Season(s) & Age group	Study type	Vaccine type Dose	Number or proportion of febrile episodes (95% Confidence interval)	Number or proportion of febrile convulsions	Primary risk Estimate (95% Confidence interval)	Total time of Adverse Event Monitoring after vaccination	Time after vaccination AE noted
Breiman 2009 Asia, S. America	2002 6-36 mos	Randomized controlled trial	LAIV 0.2 mL	LAIV + OPV Dose 1: 237/818 Placebo + OPV 234/826 LAIV 228/814	1/2,503 total vaccinated	Not specified	11 days.	Not specified
Goodman 2005 US	2002-2004 6-23 mos	Case-control	TIV	Not specified	Not specified	Hazard Ratio: Fever / Febrile Seizures. Dose1: 0.52 (0.06-4.56) / 1.17 (0.36-3.86). Dose2: 0.64 (0.15-2.74) / 1.026 (0.19-5.56)	42 days.	Not specified
Hambidge 2006 US	1991-2003 6-23 mos	Retrospective cohort, self-controlled case series	TIV	Not specified	Risk window: 22 Control window: 12 seizures Total vaccinated 45,356	Febrile Seizure Matched OR: 1.36 (0.63-2.97) Concomitant MMR excluded	14 days	21 Febrile seizures occurred after day 3 post-vaccination. Control window: 15-28 days before and after vaccination.
Lum 2010 Mostly Europe & Asia	2002-2003 11-24 mos	Randomized controlled trial	LAIV 0.2 mL	LAIV+MMR: Dose 1: 523/806; Dose 2: 195/765. Placebo + MMR: Dose 1: 229/406; Dose 2: 100/383	LAIV+MMR 1/765 Placebo + MMR 1/383	Not specified	28 days	Febrile seizure occurred 3 months after vaccination
Belshe 2007 US, Europe, ME, Asia	2004 6-59 mos	Randomized controlled trial	LAIV 0.2 mL. TIV: ≤35 mos 0.25 mL; ≥36 mos 0.5 mL	LAIV 219/3,916 TIV 78/3,936	LAIV 0/3,916 TIV 2/3,936	Not specified	Not specified	Fever within 2 days
Kavadas 2008 Canada	1991-2005 Children	Active surveillance		1 Febrile seizure after Fluzone® (Aventis) in 1991	Not specified	Not specified	Not specified	Febrile seizures occurred 1 day after vaccine.
Baxter 2010 US	2006-2007 0.5-18 Yrs.	Randomized controlled trial	TIV: <3 Yrs 15 μg 0.25 mL; >3 Yrs 15μg 0.5 mL	6 mo to <3 years: Fluarix® 16.4% (12.7-20.8) 2.9% (1.4-5.3)** Fluzone® 11.0% (7.9-14.7) 1% (0.3-2.9)**	All ages: Fluarix® 1/2,081 Fluzone® 0/1,173	Not specified	28 days.	Febrile seizures occurred 4 days after 2nd dose.

Author Year Country	Influenza Season(s) & Age group	Study type	Vaccine type Dose	Number or proportion of febrile episodes (95% Confidence interval)	Number or proportion of febrile convulsions	Primary risk Estimate (95% Confidence interval)	Total time of Adverse Event Monitoring after vaccination	Time after vaccination AE noted
Skowronski 2011 Canada	2008 6-23 mos	Randomized controlled trial	TIV 6-11 mos: 0.25 ml / 0.5 ml 12-23 mos: 0.25 ml / 0.5 ml Dose 1: 2/65 / 2/61 / 7/63 / 3/63 Dose 2: 16/65 / 1/61 / 20/61 / 14/63		0/252	Not specified	10 days	Not specified
Nolan 2010 Australia	2009 0.5-9 Yrs.	Randomized controlled trial	pA/H1N1 no adjuvant 0.25 mL (15μg) 0.50 mL (30μg) 0.25 ml / 0.5 ml Dose 1: 44/184 / 75/183 Dose 2: 32/176 / 24/168		1 FS in 18 month-old with concurrent pneumonia	Not specified	21 days.	Febrile seizure occurred 20 days after 15μg vaccine
Stavroulopoulos 2010 Greece	2009 Adults	Prospective cohort	pA/H1N1 AS03 adjuvant 0.5 mL	1/110 vaccinated 1/42 controls	0/110 vaccinated 0/42 controls	No significant difference in risk of fever between dialysis patients and controls	Not specified	Not specified
Nordin 2013 US	2002-2009 14-49 Yrs. Old Women	Retrospective cohort	TIV	13/75,906 vaccinated 227/147,992 unvaccinated	1/75,906 vaccinated 0/147,992 unvaccinated	No significant difference between vaccinated and unvaccinated	42 days	Not specified
Tennis 2011 US	2007-2009 <60 mos	Retrospective cohort	LAIV, TIV	Not specified	LAIV 1/537	Not specified	42 days	Not specified
Nazareth 2013 UK	2009 ≥9 mos	Prospective cohort	pA/H1N1 AS03 adjuvant	<5 Yrs. 9/55 5-17 Yrs. 11/63	<9 years 1/350	Not specified	201 days after last dose.	Fever reported within 7 days of vaccine
Lambert 2013 Australia	2009 0.5-18 Yrs.	Clinical trial	TIV 0.25 mL (15 μg) 0.5 mL (15 μg)	≥6 mos - <3 Yrs. Dose 1: 29/710 Dose 2: 18/710 ≥3-9 Yrs. Dose 1: 19/880 Dose 2: 10/880	1/1,976	Not specified	180 days after last vaccine	Febrile seizure day 1 after vaccination.
Stowe 2011 UK	2000-2010 <10 Yrs. With history of at least 1 convulsion	Active surveillance; Self-controlled case series	TIV, pA/H1N1 AS03 adjuvant	Not specified	2 weeks pre-vaccine: TIV 32/2,858 MIV 13/1,895 0-7 days post vaccine TIV 19/2,858 doses MIV 17/1,895 doses	IRR 7 days post Monovalent H1N1: 0.99 (0.61-1.60) Dose 1 TIV: 0.89 (0.53-1.52)	0-7 days post vaccine	

Author Year Country	Influenza Season(s) & Age group	Study type	Vaccine type Dose	Number or proportion of febrile episodes (95% Confidence interval)	Number or proportion of febrile convulsions	Primary risk Estimate (95% Confidence interval)	Total time of Adverse Event Monitoring after vaccination	Time after vaccination AE noted
Domachowske 2012 US	2009-2010 3-17 Yrs.	Randomized controlled trial	TIV 0.5 mL (15 μg)	3-4 Yrs. Vaccinated 14/294 4.8% (2.6-7.9) Control 8/281 2.9% (1.2-5.6%) 5-8 Yrs. Vaccinated 15/387 3.9% (2.2-6.3) Control 17/377 4.5% (2.6-7.1) 9-17 Yrs. Vaccinated 12/362 3.3% (1.7-5.7) Control 8/368 2.2% (0.9-4.2)	Vaccinated 1/1,055 Control 0/1,061	Not specified	180 days	Not specified
Langley, Reich 2012 Canada	2009-2010 0.5-9 Yrs.	Randomized controlled trial	pA/H1N1 AS03a: 3.75 μg AS03b: 1.9 μg No adjuvant: 7.5 or 15 μg	6 to <9 years with AS03 adjuvanted Fever 34.6-50.0%; Fever >39.0℃ 3.75 μg AS03 adjuvanted vaccine 6 mos to 5 years 8.0-18.2% 6 to <9 years 11.1%	Adjuvant vaccine 2/259 No adjuvant 0/127	Not specified	1 year.	Febrile seizure on day 105 and 266 after 2nd dose.
Armstrong 2011 Australia	2008-2010 0.5-5 Yrs.	Passive Surveillance, reports of FS, Retrospective Cohort	TIV <3 Yrs. 0.25 mL (7.5 μg) 4 Yrs. 0.5 mL (15 μg)	Fluvax® 118/209 Influvac® 19/110	62/18,816 vaccinations	Fluvax® OR of Fever 5.1 (2.9-9.2) Overall Risk of Febrile seizures: 3.3/ 1,000 doses (2.6-3.2) OR of Febrile seizures in 2010 compared to 2008: 44 (6-894) Significant Febrile Adverse Event with Fluvax® OR 8.9 (3.1-25.7)	72 Hrs.	62 Febrile seizures within 72 hours (most first dose)
Blyth 2011 Australia	2010 <5 Yrs.	Retrospective cohort	TIV <3 Yrs. 0.25 mL (7.5μg) ≥3 Yrs. 0.5 mL (15 μg)		38 FS identified	Not specified	Febrile seizure within 72 hours	Not specified
Leeb 2011 Australia	2010 ≥18 Yrs.	Retrospective survey	TIV	Fluvax® 4/156 Influvac® 4/127	Fluvax® 0/156 Influvac® 0/127	Fluvax® Adjusted OR of fever 1.63 (0.32-8.2)	72 Hrs.	Not specified

Author Year Country	Influenza Season(s) & Age group	Study type	Vaccine type Dose	Number or proportion of febrile episodes (95% Confidence interval)	Number or proportion of febrile convulsions	Primary risk Estimate (95% Confidence interval)	Total time of Adverse Event Monitoring after vaccination	Time after vaccination AE noted
Petousis-Harris 2011 New Zealand	2010 ≤5 Yrs.	Retrospective survey	TIV 15 μg	Fluvax® 33/104 Vaxigrip® 3/267	Fluvax® 1/104 Vaxigrip® 0/267	Fluvax® RR of fever 4.33 (2.4-7.7)	24 hours	Not specified
Van Buynder 2012 Canada	2010 6-59 mos	Prospective survey	TIV <3 yrs 0.25 mL ≥3 yrs 0.5 mL	56/660 vaccinated	0/660 vaccinated	Not specified	3 days	Not specified
McEvoy 2012 Australia (Perth)	2010 Adults	Not specified	TIV	Fluvax® 51/2,019 Other 2/226	0/2,245	Not specified	48 hours	Not specified
Mofleh 2012 Afghanistan	2010 Adults	Retrospective survey	pA/H1N1	144/360 vaccinated	3/360 vaccinated	Not specified	Not specified	Not specified
Petousis-Harris 2012 New Zealand	2010-2011 0.5-8 Yrs.	Retrospective survey	TIV 15μg	Fluvax® 242/865 Vaxigrip® 233/2,571 Influvac® 39/204 Fluarix® 22/438	Fluvax® 3/865 doses; Vaxigrip® 0/2,571; Influvac® 0/204 doses, Fluarix® 0/438 doses	Fluvax® Risk of Febrile seizure 35/ 10,000 doses in children 6 mos to 8 years within 24 hours of	Not specified	Not specified
Tse 2012 US	2010-2011 Not specified	Active surveillance, Self-controlled case series	TIV	Not specified	25 FS in risk interval 22 FS in control interval among 206,174 children 6-59 mos and 384,098 5-17 Yrs.	Unadjusted IRR for FS in risk window 4.0 (2.1-6.2). IRR adjusted for PCV13 same day 2.5 (1.2-4.7)	Risk window: 0-1 days post vaccination	Control window: 14-20 days after vaccination
Wood 2012 Australia	2010-2011 0.5-5 Yrs.	Cohort	TIV 0.5 mL (15 μg) pA/H1N1 no adjuvant 0.25 mL (7.25 μg) or 0.5 mL (15 μg)	66/333 vaccinated	0/333	RR fevers with CSL Fluvax® compared to others 6.5 (3.1-13.9)	Within 48 hours.	Not specified

Author Year Country	Influenza Season(s) & Age group	Study type	Vaccine type Dose	Number or proportion of febrile episodes (95% Confidence interval)	Number or proportion of febrile convulsions	Primary risk Estimate (95% Confidence interval)	Total time of Adverse Event Monitoring after vaccination	Time after vaccination AE noted
Domachowske 2013 US, Europe, Philippines	2010-2011 0.5-17 Yrs.	Randomized controlled trial	QIV, TIV 0.5 mL	6-35 mos 20% with QIV 3-5 years 12% with QIV 10% with TIV-Vic 10% with TIV-Yam 6-17 Yrs. <10% all vaccine types	6-35 mos 2/277 with QIV 3-17 years 0/915 with QIV 0/912 with TIV-Vic 0/911 with TIV-Yam	Not specified	6 mos	Febrile seizure on day 16 and 98
Greenberg 2014 US	2010-2011 0.5-9 Yrs.	Randomized controlled trial	QIV, TIV <3 Yrs. 0.25 mL >3 Yrs. 0.5 mL (15 μg)	Not specified	QIV 0/2,892 Licensed TIV 1/734 (11 month old) Unlicensed TIV 1/721 (4 year old)	Not specified	6 mos.	Febrile seizure 8 Hrs. and 1 day after.
Langley, Scheifele 2012 Canada	2010-2011 12-59 mos	Prospective cohort	TIV <3 Yrs. 0.25 mL ≥3 Yrs. 0.5 mL	Dose 1: 10/207 on day 0-1 19/207 on day 0-6	0/207	Not specified	6 mos.	Not specified
Nolan 2014 S. America, Australia, Asia	2010-2011 0.5-10 Yrs.	Randomized controlled trial	pA/H1N1 AS03 1.9 μg No adjuvant <3 Yrs. 0.25 mL(7.5 μg) >3 Yrs. 0.5 ml (15 μg)	Dose 1 Adjuvanted vaccine + placebo 310/1,356 2 Doses of Adjuvanted vaccine 300/1,336 6 mos to <6 years 19.0% (16.9-21.2) No adjuvant 176/1,327	15 febrile convulsions Adjuvanted + placebo 6/1,356 2 doses of Adjuvanted vaccine 4/1,336 No adjuvant 5/1,327	Not specified	1 year	Febrile seizure on day 42.
Stockwell 2014 US	2011-2012 6-23 mos	Prospective cohort	TIV	TIV and PCV13 64/170, TIV 12/159, PCV13 8/84	0/530 children	Adjusted RR fever TIV and PCV13 vs TIV alone 2.69 (1.3-5.6)	7 days	Not specified
Halasa 2014 US	2010-2012 6-35 mos	Randomized controlled trial	TIV 0.25 mL(7.5 μg) 0.5 mL (15 μg)	Not specified	0/243	Not specified	Not specified	Not specified

** High fever.

1-cca: chick cell agglutinating units; S. America: South America; MIV: monovalent; TIV-Vic: TIV-B/Victoria; TIV-Yam: TIV-B/Yamagata; MIV: Monovalent inactivated influenza vaccine; TIV: Trivalent inactivated influenza vaccine; QIV: Quadrivalent inactivated influenza vaccine; LAIV: Live attenuated influenza vaccine; IM: Intramuscular; SC: Subcutaenous; FS: Febrile Seizure; OR: Odds Ratio; IRR: Incidence rate ratio; Mos: months; OPV: oral polio vaccine; Yrs: Years; ED: Emergency Department.

Appendix 5. Epidemiological Evidence for Association between Influenza Vaccines and Guillain-Barré Syndrome by Influenza Season

	First author	Pub year	Study type	Influenza season(s)	Country	Type of vaccine	# of cases in each group	Primary risk estimate (95% confidence interval)	Finding in children
1	Schonberger	1979	Retrospective cohort	1976–77	US	mH1N1	363 GBS cases within 6 wks after vaccination	RR: 9.2 (8.2–10.3)	NA
2	Johnson	1982	Retrospective cohort	1976–77	US	Not specified	98 cases	Incidence not higher than previous years	NA
3	Hurwitz	1981	Retrospective cohort	1978–79	US	Not specified	12 GBS cases within 8 wks after vaccination, 393 unvaccinated	RR: 1.4 (0.7–2.7)	NA
4	Kaplan	1982	Prospective cohort	1979–80	US	TIV	7 GBS cases vaccinated, 412 unvaccinated (1979–80); 12 cases vaccinated, 347 unvaccinated (1980–81)	RR: 0.6 (0.45–1.32) 1979–80; 1.4 (0.8–1.76) 1980–81	NA
5	Roscelli	1991	Retrospective cohort	1980–88	US	Not specified	289 GBS cases	No temporal or seasonal differences	NA
6	Stowe	2009	Self-controlled case series	1990–05	UK	Not specified	12 GBS cases within 90 days after vaccination	IRR: 0.76 (0.41–1.40)	NA
7	Hughes	2006	Self-controlled case series	1992–00	UK	Not specified	3 GBS cases within 42 days after vaccination, 225 cases unvaccinated	RR: 0.99 (0.32–3.12)	NA
8	Lasky	1998	Retrospective cohort	1992–94	US	Not specified	19 cases vaccinated within 6 wks prior to GBS onset, 148 non-vaccine-associated cases	RR: 1.7 (1.0–2.8)	NA
9	Juurlink	2006	Self-controlled case series	2000–01	Canada	Not specified	51 GBS cases within 2–7 wks after vaccination, 141 in control period between 26 and 43 wks	IRR: 1.45 (1.05–1.99)	NA
10	Baxter	2013	Self-controlled case series	1995–06	US	TIV	18 cases vaccinated within 6 wks prior to GBS onset, 92 cases vaccinated within prior 9 months	OR: 1.1 (0.4–3.1)	NA
11	Burwen	2010	Self-controlled case series	2000–01	US	TIV	84 GBS cases within 6 wks after vaccination, 80 in control period of wks 9–14	IRR: 1.04 (0.76–1.43)	NA
12	Greene	2010	Retrospective cohort	2005–08	US	TIV	12, 17, 23 GBS cases within 42 days after vaccination (by year), compared to 14.4, 15.1, 16.7 expected cases based on historical risk periods	RR: 0.83, 1.13, 1.37 (by year, no Cis provided)	NA

	First author	Pub year	Study type	Influenza season(s)	Country	Type of vaccine	# of cases in each group	Primary risk estimate (95% confidence interval)	Finding in children
13	Ho	2012	Retrospective cohort	2008–09	Taiwan	Inactivated, split non adjuvanted	17 GBS cases vaccinated, 12 unvaccinated (1 year of follow-up)	OR: 1.64 (0.77–3.49)	NA
14	Dieleman	2011	Case–control	2009–10	Denmark, France, Netherlands, Sweden UK	mH1N1 (AS03-adjuvanted)	104 GBS cases each to 1+ controls	OR: 1.0 (0.3–2.7)	9 children with GBS included, no risk estimate provided
15	Salmon	2013	Self-controlled case series, meta-analysis	2009–10	US	mH1N1	54 GBS cases within 42 days after vaccination, 23 within 50–91 days	IRR: 2.35 (1.42–4.01)	2.33 (0.65–10.46)
16	Dodd	2013	Self-controlled case series, meta-analysis	2009–10	Australia, Canada, China, Denmark, Finland, Netherlands, Singapore, Spain, UK, US	Variable – adjuvanted and non-adjuvanted	risk interval within 42 days after vaccination	IRR: pooled 2.86 (1.88–4.34); meta-analytic 2.42 (1.58–3.72)	Trend of increasing risk with increasing age; <19 = 0.73 (0.16–3.46)
17	Huang	2013	Self-controlled case series	2009–10	Taiwan	TIV with and without adjuvant	5 GBS cases within 42 days after vaccination, 1 unvaccinated	IRR: 3.81 (0.43–33.85)	NA
18	Prestel	2014	Self-controlled case series	2009–10	Germany	mH1N1 (AS03-adjuvanted) and seasonal	18 GBS cases in risk period of 5–42 days after vaccination, 11 in control period of 43–150 days	IRR: 2.96 (106–8.25)	1 case in risk window for child <10, no cases in comparison window
19	Grimaldi-Bensouda	2011	Case–control	2007–10	France	Not specified	145 GBS cases to 1080 controls	OR: 1.22 (0.45–3.32)	NA
20	Galeotti	2013	Case–control	2010–11	Italy	Inactivated, mostly non-adjuvanted	140 GBS cases to 308 controls	OR: 3.8 (1.3–10.5)	NA
21	Greene	2013	Self-controlled case series	2009–11	US	MIV/TIV	18 GBS cases among 1.27 million 2009–10 MIV and 2.8 million 2010–11 TIV	OR: 1.54 (0.59–3.99)	NA
22	Kwong	2013	Self-controlled case series	1993–2011	Canada	Non-adjuvanted TIV	69 GBS cases within 6 wks of vaccination, 251 during control interval of 9–42 wks	IRR: 1.52 (1.17–1.99)	1.66 (0.46–6.03)
23	McCarthy	2013	Self-controlled case series	2009–11	US	H1N1, 2009–10 TIV, 2010–11 TIV	6 GBS cases within 42 days of vaccination, 3 in comparison window of 43–84 days(H1N1); 11 cases within 42 days of vaccination, 7 cases in comparison window (2009–10 TIV); 14 cases within 42 days of vaccination, 14 days in comparison window (2010–11 TIV)	IRR: 2.0 (0.50–8.0) H1N1; 1.57 (0.61–4.05) 2009–10 TIV; 1.00 (0.45–2.23) 2010–11 TIV	NA
24	Kawai	2014	Retrospective cohort	2012–13	US	Non-adjuvanted TIV and LAIV	14 GBS cases within 42 days after vaccination, 102 in historical control group	RR: 0.5 (0.3–0.9) in TIV; LAIV one case in risk and none in control window	NA

Note: There are additional publications which include subsets of the data published from the US studies in 1976–77 ([216], line 1) and 2009–10 ([217], line 15) and consequently these studies are not listed in Table.

Appendix 6. Epidemiological Evidence for Association between Influenza Vaccines and Multiple Sclerosis by Study Type

	First author	Pub year	Study type	Influenza season(s)	Country	Type of Vaccine	# of cases in each group	Primary risk estimate (95% confidence interval)	Finding in children	Incident or relapse
1	DeStefano	2003	Case–control	Not specified	US	Not specified	73 cases, 177 controls	OR: 0.7 (0.5–1.1) ever vaccinated before MS index date vs not	NA	Incident
2	Hernán	2004	Case–control	Not specified	UK	Not specified	Vaccinated: 10 cases, 153 controls. Reference: 153 cases, 1508 controls.	OR: 1.0 (0.5–2.0) vaccinated within 3 yrs before MS index date vs not	NA	Incident
3	Ramagopalan	2009	Case–control	Not specified	Canada	Not specified	14362 cases, 7671 controls	OR: 1.02 (0.96–1.09) vaccinated vs not, adjusted for age and sex	NA	Incident
4	Bardage	2011	Retrospective cohort	2009–2010	Sweden	Pandemic A/H1N1, AS03	3795 cases	HR: 0.93 (0.68–1.26) vaccinated vs not, adjusted for age, sex, SES, healthcare consumption	Included large numbers of children but results not stratified by age	Incident
5	Ho	2012	Retrospective cohort	2008–2009	Taiwan	Unadjuvanted TIV	8 cases in persons aged 65+ yrs	Adjusted OR: 0.35 (0.07–1.77) vaccinated within 1 yr before vs not	NA	Incident
6	Persson	2014	Prospective cohort	2009–2010	Sweden	Pandemic A/H1N1, AS03	1003	Adjusted OR: 1.04 (0.95–1.15)	Included large numbers of children but results not stratified by age	Incident
7	Myers	1977	Randomized controlled trial	Not specified	US	Whole BIV	33 vaccinated, 33 placebo, 22 no injection controls	Relapse rate per patient year: 0.5 vaccinated, 0.5 placebo, 0.7 untreated control	NA	Relapse
8	Bamford	1978	Randomized controlled trial	1976–1977	US	Bivalent swine flu	65 vaccinated and 62 controls	No differneces in neurological symptoms or reoccurance by group	NA	Relapse
9	Miller	1997	Randomized controlled trial	1993	US	Seasonal	49 vaccinated and 54 controls	Annual rate: 0.45 vaccinated, 0.22 placebo; no statistically signifiant difference	NA	Relapse
10	Mokhtarian	1997	Randomized controlled trial	1993–1994	US	TIV	11 vaccinated and contrors	MS relapse and Extended Disability Status Score not different between groups	NA	Relapse
11	Confavreux	2001	Case-crossover	1993–1997	France, Spain, Switzerland	Not specified	23 vaccinated in yr before relapse	RR: 1.08 (0.37–3.10) vaccinated within 2 months before relapse vs control period	NA	Relapse
12	Auriel	2011	Cohort	2009–2010	Israel	Seasonal and pandemic A/H1N1	24 vaccinated with seasonal and H1N1, 14 seasonal only, 11 H1N1 only, 52 not vaccinated	No new neurological symptoms in any vaccinated persons; Extended Disability Status Score not different between groups	NA	Relapse

Appendix 7. Epidemiological Evidence for Association between Influenza Vaccines and Narcolepsy by Country

First author	Pub year	Country	Influenza season(s)	Type	Vaccine	Adjuvant	Population size	# of cases	Age group	Study type	Primary risk estimate (95% confidence interval)
Nohynek	2012	Finland	2009–2010	pA/H1N1	Pandemrix	AS03	5.3 million	67	4–19 yrs	Retrospective cohort	IRR: 12.7 (6.1–30.8) within 8 months of vaccine vs unvaccinated
Partinen	2012	Finland	2002–2010	pA/H1N1	Pandemrix	AS03	not specified	54 (50 vaccinated)	<17	Modified cohort	IRR: 17 (no CI or p) 2010 vs 2002–2009
MPA	2011	Sweden	2009–2010	pA/H1N1	Pandemrix	AS03	57% Swedish pop	81 (69 vaccinated)	<19 yrs	Retrospective cohort	IRR: 6.6 (3.1–14.5) vaccinated vs not
Szakács	2013	Sweden	2000–2010	pA/H1N1	Pandemrix	AS03	20% Swedish pop	36	2–17 yrs	Modified cohort	IRR: 25 ($p < 0.000001$) during vaccination period vs before
Persson	2014	Sweden	2009–2011	pA/H1N1	Pandemrix	AS03	61% Swedish pop	126	≤20 yrs	Prospective cohort	HR: 2.92 (1.78–4.79) vaccinated vs not
O'Flanagan	2014	Ireland	2009–2010	pA/H1N1	Pandemrix	AS03	906,280	24 (19 vaccinated)	<20 yrs	Retrospective cohort	IRR: 13.9 (5.2–37.2) vaccinated vs not
Miller	2013	England	2009	pA/H1N1	Pandemrix	AS03	Not specified	75	4–18 yrs	Case-coverage	OR: 16.2 (3.1–84.5) vaccinated within 6 months before vs not
										Self-controlled case series	IRR: 9.9 (2.1–47.9) within 3–6 months of vaccine vs control period
Winstone	2014	England	2008–2011	pA/H1N1	Pandemrix	AS03	16 hospitals	75 (11 vaccinated)	3–18 yrs	Retrospective cohort	not specified
Dauvilliers	2013	France	2005+	pA/H1N1	Pandemrix or Panenza	AS03 or none	Not specified	59 cases vs 135 controls	<18 yrs	Matched case–control	OR: 6.5 (2.1–19.9) vaccinated vs not
									18+ yrs		OR: 4.7 (1.6–13.9) vaccinated vs not
Heier	2013	Norway	2009–2010	pA/H1N1	Pandemrix	AS03	470,000 vaccinated	58 vaccinated	4–19 yrs	Retrospective cohort	Minimum IR: 10/100,000 within 1 year of vaccine
				NA	NA	NA	approx. 470,000 not	5 not			IR: 0.5–1/100,000 unvaccinated
McCarthy	2013	US	2009–2010	pA/H1N1	Not specified	Not specified	312,914 doses	2 (risk), 19 (comp)	≤24 yrs	Self-controlled case series	IRR: 0.53 (0.12–2.27) within 90 days of vaccine vs historical comp
							225,343 doses	23 (risk), 215 (comp)	≥25 yrs		IRR: 0.95 (0.62–1.46) within 90 days of vaccine vs historical comp

First author	Pub year	Country	Influenza season(s)	Type	Vaccine	Adjuvant	Population size	# of cases	Age group	Study type	Primary risk estimate (95% confidence interval)
Duffy	2014	US	2009–2010	pA/H1N1	pdm09 strain	Not specified	650,995	0 within 180 days	<30 yrs	Retrospective cohort	0 observed compared to 6.52 expected from published IR estimates
			2010–2011	seasonal			870,530	2 within 180 days			2 observed compared to 8.83 expected from published IR estimates
Montplaisir	2014	Canada	2009–2010	pA/H1N1	Arepanrix	AS03	Quebec: 7,817,449	12 (5 vaccinated)	.5–20 yrs	Retrospective cohort	IRR: 6.39 (1.60–23.38) vaccinated vs not
								8		Self-controlled case series	IRR: 2.96 (0.71–12.39) within 16 weeks of vaccine vs not
								8 (6 vaccinated)		Case–control	OR: 3.21 (0.37–90.37)
Tsai	2011	>25 countries	Until 7/10	pA/H1N1	Focetria	MF59	23.26 million doses	0	All ages	Retrospective cohort	not specified
		115 trials	Not specified	All Novartis influenza vaccines			79,004	0		Retrospective cohort	not specified
Wijnans	2013	Sweden	2000–2010	Vaccine not part of analysis			9 million	60 after, 60 before	5–19 yrs	Retrospective cohort	IRR: 7.5 (5.2–10.7) after 9/09 vs before 4/09
		Finland					.5 million	67 after, 25 before			IRR: 6.4 (4.2–9.7) after 9/09 vs before 4/09
		Denmark					5.5 million	20 after, 70 before			IRR: 1.9 (1.1–3.1) after 9/09 vs before 4/09
		Netherlands					1 million	1 after, 2 before			IRR: 5.7 (0.6–54) after 9/09 vs before 4/09
		UK					3.5 million	4 after, 46 before			IRR: 0.9 (0.3–2.5) after 9/09 vs before 4/09
		Italy					6 million	2 after, 11 before			IRR: 1.1 (0.2–4.9) after 9/09 vs before 4/09
ECDC	2012	Sweden and Finland	2009–2010	pA/H1N1	Pandemrix	AS03	Not specified	4 cases, 23 controls	≤18	Case–control	OR: 15.8 (1.6–infinity) 8–42 days after vaccine
								29 cases, 214 controls			OR: 11.4 (1.9–infinity) 43–180 days after vaccine
		Denmark, Netherlands, UK, Italy and Norway						1 case, 3 controls			OR: 0.6 (0.0–19.7) 8–42 days after vaccine
								8 cases, 11 controls			OR: 9.5 (1.1–461) 43–180 days after vaccine

Appendix 8. Epidemiological Evidence for Association between LAIV and Adverse Events

First author	Pub year	Country	Study years	Age	Study type	Vaccine manufacturer (name of vaccine)	Number of doses studied	Size of study groups	Time window studied	Fever and local reactions	Systemic reactions	Asthma and Wheezing
Rudenko	1993	Russia	1989–1991	7–14 yrs	Randomized controlled trial	Russian	1	>100/group	Not specified	0.6% (2/323) LAIV, 0.7% (2/278) placebo, 1.8% IIV (5/271 in 7–10 yrs, 8/435 in 11–14 yrs)	Not specified	Not specified
Slepushkin	1993	Russia	1987–1988	8–15 yrs	Randomized controlled trial	IVSP, Leningrad	2, 4 weeks apart	345 (97 LAIV)	4 days	Fever: 2/95 LAIV, 0/78 placebo (Dose 2)	Not specified	Not specified
Edwards	1994	USA	1985–1990	1–65 yrs	Randomized controlled trial	not specified	Not specified	5210	Not specified	Redness: 8.3% placebo, 10.5% IIV; Induration: 7.1% placebo, 12.1% IIV; Tenderness: 36% placebo, 51.1% IIV ($p < 0.00005$)	Rhinorrhea: 26.2% LAIV, 19.8% control ($p < 0.00005$); Lethargy: 21.7% LAIV,18.4% IIV, 16.7% placebo ($p < 0.00005$ vs LAIV); Sore throat: 20.5% LAIV, 9.8% placebo ($p < 0.05$); Myalgia: 15.3% LAIV ($p < 0.05$ vs placebo), 14.1% IIV, 13.3% placebo; Headache: LAIV 22.6% ($p < 0.005$ vs placebo), 20.7% IIV, 19.7% placebo; Cough and GI: no difference.	Not specified
Swierkosz	1994	USA	Not specified	2–22 months	Controlled trial	L. Potash	3, 2 months apart	17 LAIV, 5 placebo	11 days	Fever: 3/17 vaccine, 0/5 placebo (Dose 1)	Cough: 1/17 vaccinees, 3/5 placebos; Rhinorrhea: 9/17 vaccinees	Not specified
Gruber	1996	USA	1991	6–18 months	Controlled trial	Wyeth-Ayerst	1	182	10 days	Fever: 5/44 H1N1, 13/45 H3N2, 12/47 bivalent, 10/44 control	Cough: 23/44 H1N1, 23/45 H3N2, 19/47 bivalent, 24/44 control; Rhinorrhea: 32/44 H1N1, 35/45 H3N2, 35/37 bivalent, 30/44 control	Not specified

First author	Pub year	Country	Study years	Age	Study type	Vaccine manufacturer (name of vaccine)	Number of doses studied	Size of study groups	Time window studied	Fever and local reactions	Systemic reactions	Asthma and Wheezing
Rudenko	1996	Russia, Cuba, Khazakstan	1986–1991	3–14 yrs	Randomized controlled trial	not specified	2, 21–28 days apart	521 LAIV-L, 545 placebo	7 days	Fever: no difference	Cough and Rhinorrhea: no difference	Not specified
Belshe	1998	USA	1995–96	15––71 months	Randomized controlled trial	Aviron	1 vs 2	1314 (2 dose), 288 (1 dose); 2:1 LAIV to placebo	10 days	Fever: 15% vaccine, 11% placebo ($p = 0.05$) (day 2 – 6.5% vs 1.6% $p < 0.001$);	Rhinorrhea: 58% vaccine, 47% placebo ($p < 0.001$); Lethargy: 16% vaccine, 12% placebo ($p = 0.06$)	Not specified
King, Jr.	2001	USA	Not specified	1–17 yrs	Randomized controlled trial	Aviron	2	24 HIV+, 25 HIV−	not specified	Fever: no difference	Cough: LAIV 30%, placebo 38%; Rhinorrhea: LAIV 39%, placebo 21%; Lethargy: LAIV 13%, placebo 0; Irritability: LAIV 17% placebo 13%;	Not specified
Piedra	2002	USA	1996–2000	15–71 months	Randomized controlled trial	Aviron	Not specified	Yr 1: 1070 LAIV, 532 placebo	42 days (10 acute)	Fever: OR 5.23 (2.48–11.0) (Day 2) (Dose 1), no difference other days (Yr 1); OR 4.43 (1.02–19.28) (Day 3) (Yr 2)	Rhinorrhea: OR 1.61 (1.3–1.99) (Dose 1), 1.29 (1.02–1.65) (Dose 2) (highest days 2–3, persisted day 8–9); Lethargy: OR 2.91 (1.51–5.58) (Day 2); Irritability: OR 1.81 (1.15–2.85) (Day 2); GI: OR 1.78 (1.05–3.01) vomiting, OR 2.0 (1.10–3.65)	Not specified
Redding	2002	USA	1997–1998	9–17 yrs	Randomized controlled trial	not specified	Not specified	24 with asthma/group	7 days before, 28 days after	not specified	not specified	No difference
Bergen	2004	USA	1999–2000	1–18 yrs	Randomized controlled trial	MedImmune	2 in 1–8 yrs; 1 in 9–18 yrs	9689; 2:1 LAIV to placebo 8.8% previous wheeze or asthma. ***Used 90% CI (not 95).	42 days	Not specified	URI: 88.9 visits/1000 person-months vaccine, 68.9 visits/1000 person-months placebo in 18–35 month olds.	RR 4.06 (90% CI 1.29–17.86) in 18–35 month olds (7 of 16 with pre-existing asthma). In all children with h/o previous wheeze, RR 1.11 (90%CI, 0.59–2.14).

First author	Pub year	Country	Study years	Age	Study type	Vaccine manufacturer (name of vaccine)	Number of doses studied	Size of study groups	Time window studied	Fever and local reactions	Systemic reactions	Asthma and Wheezing
Piedra	2005	USA	1997–2002	1.5–18 yrs	Clinical trial	MedImmune	1/yr	18,780 doses in 11,096 children	42 days (14 acute)	Not specified	Not specified	no increased risk in visits in 0–14 days, 1.5–4 yrs had increased wheezing days 15–42 (RR 2.85; 1.01–8.03) (Yr 1) 10% with mild asthma/RAD
Vesikari	2006	Finland	1999–2000	9–36 months	Randomized controlled trial	MedImmune	1	98 LAIV, 99 placebo	42 days (10 reactogenicity)	Fever: 51% vaccine, 51% placebo (>38C), 4% vs 10.4% (>/=39.1), no difference in rates	Cough, Rhinorrhea, Lethargy, Irritability, and GI: no difference	not specified *1 confirmed case of vaccine virus transmission from vaccinee to placebo recipient.
Fleming	2006	13, mostly Europe	2002–2003	6–17 yrs	not specified	Wyeth-Ayerst	Not specified	1114 LAIV, 1115 TIV; all with asthma	42 days (15 reactogenicity)	Fever: no difference	Rhinorrhea: 66.2% LAIV, 52.5% TIV ($p < 0.0001$); Headache: greater in LAIV vs TIV; Cough, Lethargy, Irritability, and GI: no difference	19.5% LAIV, 23.8% TIV ($p = 0.02$) (15 days)
Ashkenazi	2006	9 in Europe	2002–2003	6–71 months history of recurrent RTI	Randomized trial	Wyeth-Ayerst	2, 35 days apart	LAIV 1101, TIV 1086; all with RTI, 40% wheezing, 23% asthma	11 days (42 wheezing)	Fever: no difference. Local rxns: 31.6% TIV (Dose 1), 28.9% (Dose 2); Pain: 24.2% TIV (Dose 1), 23.3% (Dose 2).	Rhinorrhea: 68.3% LAIV, 55.1% TIV ($p < 0.0001$) (Dose 1), 52.1% LAIV, 44.4% TIV ($p < 0.0001$) (Dose 2); Decreased appetite: LAIV 23.9%, TIV 19.8% ($p = 0.031$) (Dose 2); Cough, Lethargy, and Irritability: no difference	no difference * likely documentation of transmission
Belshe	2007	16: USA, ME, Europe, Asia	2004–2005	6–59 months	Randomized trial	MedImmune, Aventis Pasteur	1 or 2	4179 LAIV, 4173 IIV	42 days	Fever: 5.4% LAIV, 2.0% TIV ($p < 0.001$) (>37.8C) (Day 2) (Dose 1), no difference (Dose 2)	Rhinorrhea: 57% LAIV, 46.3% TIV	3.2% LAIV, 2.0% IIV (<2 yrs) (Dose 1)
Gaglani	2008	USA	1998–2002	1.5–18 yrs	Reanalysis of Piedra trial data	Aviron, MedImmune	not specified	430–656/year; all with asthma, RAD or wheezing	42 days	not specified	not specified	Asthma/wheezing: no increase in health care utilization in the 0–14 days or 0–42 period after vaccination vs reference times

First author	Pub year	Country	Study years	Age	Study type	Vaccine manufacturer (name of vaccine)	Number of doses studied	Size of study groups	Time window studied	Fever and local reactions	Systemic reactions	Asthma and Wheezing
Levin	2008	USA	2004–2005	5–18 yrs	Randomized controlled trial	MedImmune, Aventis Pasteur	1	122 LAIV, 121 TIV	42 days	Local rxns: 23% TIV, 0% LAIV.	Pulmonary: LAI 32%, TIV 26%; Nasopharyngeal: 52% LAIV, 31% TIV; Abdominal: 16% LAIV, 8% TIV; Constitutional: no difference	Not specified
Neto	2009	S. Africa, Brazil, Argentina	2001–2003	6–36 months	Randomized controlled trial	MedImmune	Not specified	3200; 2:2:1:1	11 days	Fever: no difference	Cough: 50.3% LAIV, 58.2% placebo ($p < 0.004$); Rhinnorea, Lethargy, Irritability, and GI: no difference	Not specified
Breiman	2009	7 in S. America and Asia	2002	6–36 months	Randomized controlled trial	MedImmune and Wyeth	2	832 LAIV+OPV, 836 placebo+OPV, 835 LAIV	11 days	Fever: no difference in rates between 3 groups	Rhinorrhea: 70% LAIV+OPV, 62.7% placebo+OPV, 67.2% LAIV alone ($p = 0.006$) (Dose 1); Lethargy: 14.7% LAIV+OPV, 17.3% placebo+OPV, 12.4% LAIV alone ($p = 0.017$) (Dose 1);	Not specified
Lum	2010	13, mostly Europe and Asia	2002–2003	11–24 months	Randomized controlled trial	MedImmune and Wyeth	2, MMR with 1st	819 LAIV, 414 Placebo	27 days	Fever: 49.9% LAIV, 41.7% ($p < 0.001$) (>37.5C) (Dose 1), LAIV 0, placebo 0.8% ($p = 0.035$) (40C) (Dose 2)	Rhinorrhea: LAIV 70.1%, placebo 51.6% ($p < 0.001$); Decreased appetite: 33.6% LAIV, 27.7% placebo ($p = 0.036$);	Not specified
Mallory	2010	USA	2009	2–17 yrs	Randomized controlled trial	MedImmune	2	260 LAIV, 65 placebo	15 days (8 fever)	Fever: 1.5% LAIV, 1.5% placebo (≥38.3)	Cough, Rhinorrhea, Lethargy: no difference	Not specified
Tennis	2011	USA	2007–2009	2–5 yrs	Retrospective cohort	not specified	Not specified	633 yr1, 2412 yr2 asthma and wheezing; 12, 89 immunocomp.	42 days	Not specified	Not specified	Not specified no increase in hospitalizations LAIV vs TIV
Carr	2011	USA	2008–2009	2–21 yrs	Randomized controlled trial	not specified	Not specified	28 LAIV, 27 TIV	28 days	Fever: LAIV 0%, TIV 7.4% (Dose 1) (Days 0–10), 3.6% LAIV, 14.8% TIV (Days 0–28). Local rxns: 14.8% TIV (Days 0–10), 18.5% (Days 0–28).	Cough: LAIV 7.1%, TIV 18.5% (Days 0–10), 10.7% LAIV, 18.5% TIV (Days 0–28) (Dose 1); Rhinorrhea: 35.7% LAIV, 33.3% TIV (Days 0–10), 42.9% LAIV, 33.3% TIV (Days 0–28) (Dose 1); Irritability: 10.7% LAIV, 3.7% TIV.	Not specified

First author	Pub year	Country	Study years	Age	Study type	Vaccine manufacturer (name of vaccine)	Number of doses studied	Size of study groups	Time window studied	Fever and local reactions	Systemic reactions	Asthma and Wheezing
Halasa	2011	USA	2005–2007	5–17 yrs	Randomized controlled trial	MedImmune	1	10 LAIV, 10 placebo	42 days	Fever: 11% LAIV, 10% placebo (≥37.8C) (Days 0–10)	Cough: 11% LAIV, 10% placebo (Days 0–10); Rhinorrhea: 78% LAIV, 20% placebo ($p = 0.02$) (Days 0–10)	Not specified
Tennis	2012	USA	2009–2010	2–5 yrs	Retrospective cohort	not specified	Not specified	3457 asthma, 5821 wheezing, 361 immunocomp.	42 days	Not specified	Not specified	Not specified No increase in hospitalizations LAIV vs TIV
Block	2012	USA	2009–2010	2–17 yrs	Randomized controlled trial	MedImmune	2 in 2–8 yrs; 1 in 9–17 yrs	1385 QLAIV, 464 T/LAIV B-Yamagata, 463-T/LAIV B-Victoria	10 days	Fever: 5.1% QLAIV, 3.1% TLAIV ($p = 0.04$) (T> 38) (2–8 yrs), no difference (T> 38.5), QLAIV 1.2%, TLAIV 0.3% (T>39.0C)	Irritability: no difference	Not specified
Baxter	2012	USA	2003–2008	5–17 yrs	Prospective cohort	MedImmune	1	53369 LAIV, 48683 TIV doses in 43702; 53366 unvaccinated	42 days	Not specified	Not specified	Lower in LAIV vs TIV
Toback	2013	USA	2007–2010	24–59 months	Prospective cohort	not specified	Not specified	28226 LAIV, 27937 TIV, 25981 unvaccinated	42 days	Not specified	Not specified	Hospitalization (180 days) lower in LAIV vs TIV
Kulkarni	2013	India	2009	≥3 yrs	Retrospective surveillance	Serum Institute of India	1	7565	7 days based on recall 1 year later		Cough: 0.05%; Runny nose: 0.32%; Stuffy nose: 0.03%; Sneezing: 0.11%	0.03%
Boikos	2014	Canada	2012–2013	2–18 yrs	Prospective cohort Self controlled	MedImmune	1 (2 in 2 subjects)	168 children with CF	28 days	Fever: 38% at risk, 9% not, RR 4.27 (2.54–7.18)	Cough: 23% at risk, 13% not, RR 1.77 (1.1–2.86); Runny nose: 33% at risk D0–6; 44% at risk D0–28, 17% not, RR 2.64 (1.81–3.86); Nasal congestion: 40% at risk, 14% not, RR 2.91 (1.91–4.45); Ab pain: 20% at risk, 4% not, RR 4.86 (2.22–10.65); Vomiting: 14% at risk, 2% not, RR 7.67 (2.35–25.05); also significant for diarrhea (13 vs 3%) and nausea (13 vs 5%).	Wheezing: 8% at risk, 2% not (1.26–14.93)

References

[1] Poehling KA, Edwards KM, Griffin MR, Szilagyi PG, Staat MA, Iwane MK, et al. The burden of influenza in young children, 2004–2009. Pediatrics 2013;131(2):207–16.
[2] Harris T, Wong K, Stanford L, Fediurek J, Crowcroft N, Deeks S. Did narcolepsy occur following administration of AS03-adjuvanted A(H1N1) pandemic vaccine in Ontario Canada? A review of post-marketing safety surveillance data. Euro Surveill 2014;19(36).
[3] Halsey NA. The science of evaluation of adverse events associated with vaccination. Semin Pediatr Infect Dis 2002;13(3):205–14.
[4] Tozzi AE, Asturias EJ, Balakrishnan MR, Halsey NA, Law B, Zuber PL. Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use. Vaccine 2013;31(44):5041–6.
[5] World Health Organization/Global Vaccine Safety. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO AEFI causality assessment classification; 2013. Available online at: http://www.who.int/vaccine_safety/publications/gvs_aefi/en/ [accessed 26.05.15].
[6] Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice. Epidemiol Infect 2011;139(12):1805–17.
[7] Institute of Medicine. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press; 2012.
[8] Girard MP, Plotkin SA. HIV vaccine development at the turn of the 21st century. Curr Opin HIV AIDS 2012;7(1):4–9.
[9] Polack FP. Atypical measles and enhanced respiratory syncytial virus disease (ERD) made simple. Pediatr Res 2007;62(1):111–5.
[10] Wood RA, Berger M, Dreskin SC, Setse R, Engler RJ, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics 2008;122(3):e771–7.
[11] CIOMS. Frequency of adverse drug reactions. Guidelines for preparing core clinical safety information on drugs report from CIOMS working group III, Geneva; 1995.
[12] Dormitzer PR, Tsai TF, Del Giudice G. New technologies for influenza vaccines. Hum Vaccin Immunother 2012;8(1):45–58.
[13] Huber VC. Influenza vaccines: from whole-virus preparations to recombinant protein technology. Expert Rev Vaccines 2014;13(1):31–42.
[14] Vajo Z, Kosa L, Szilvasy I, Pauliny Z, Bartha K, Visontay I, et al. Yearly licensing studies from 1997 to 2007 of the inactivated whole-virus seasonal influenza vaccine fluval – a useful approach to pandemic vaccine development even in less well developed countries? Influenza Other Respir Viruses 2008;2(6):221–8.
[15] Loew-Baselli A, Pavlova BG, Fritsch S, Poellabauer EM, Draxler W, Kistner O, et al. A non-adjuvanted whole-virus H1N1 pandemic vaccine is well tolerated and highly immunogenic in children and adolescents and induces substantial immunological memory. Vaccine 2012;30(41):5956–66.
[16] Waddington CS, Walker WT, Oeser C, Reiner A, John T, Wilkins S, et al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. BMJ 2010;340:c2649.
[17] Nicholson KG, Abrams KR, Batham S, Clark TW, Hoschler K, Lim WS, et al. Immunogenicity and safety of a two-dose schedule of whole-virion and AS03A-adjuvanted 2009 influenza A (H1N1) vaccines: a randomised, multicentre, age-stratified, head-to-head trial. Lancet Infect Dis 2011;11(2):91–101.
[18] Kulkarni PS, Manjunath K, Agarkhedkar S, Group of SII IIV Studies. Safety and immunogenicity of an adjuvanted whole virion, inactivated A (H1N1) 2009 influenza vaccine in young and elderly adults, and children. Vaccine 2012;31(1):20–2.
[19] Liang XF, Wang HQ, Wang JZ, Fang HH, Wu J, Zhu FC, et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2010;375(9708):56–66.
[20] Treanor JJ, El Sahly H, King J, Graham I, Izikson R, Kohberger R, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: a randomized, placebo-controlled trial. Vaccine 2011;29(44):7733–9.
[21] van der Velden MV, Fritz R, Pöllabauer EM, Portsmouth D, Howard MK, Kreil TR, et al. Safety and immunogenicity of a vero cell culture-derived whole-virus influenza A(H5N1) vaccine in a pediatric population. J Infect Dis 2014;209(1):12–23.
[22] Sansyzbay AR, Erofeeva MK, Khairullin BM, Sandybayev NT, Kydyrbayev ZK, Mamadaliyev SM, et al. An inactivated, adjuvanted whole virion clade 2.2 H5N1 (A/Chicken/Astana/6/05) influenza vaccine is safe and immunogenic in a single dose in humans. Clin Vaccine Immunol 2013;20(8):1314–9.
[23] Hoa LK, Hiep LV, Be LV. Development of pandemic influenza vaccine production capacity in Viet Nam. Vaccine 2011;29(Suppl. 1):A34–6.
[24] Li H, Guo XJ, Ye XF, Jiang H, Du WM, Xu JF, et al. Adverse drug reactions of spontaneous reports in shanghai pediatric population. PLOS ONE 2014;9(2):e89829.
[25] Reisinger KS, Block SL, Izu A, Groth N, Holmes SJ. Subunit influenza vaccines produced from cell culture or in embryonated chicken eggs: comparison of safety, reactogenicity, and immunogenicity. J Infect Dis 2009;200(6):849–57.
[26] Rowhani-Rahbar A, Klein NP, Baxter R. Assessing the safety of influenza vaccination in specific populations: children and the elderly. Expert Rev Vaccines 2012;11(8):973–84.
[27] Rowhani-Rahbar A, Klein NP, Dekker CL, Edwards KM, Marchant CD, Vellozzi C, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine 2012;31(1):271–7.
[28] Cook IF. An evidence based protocol for the prevention of upper arm injury related to vaccine administration (UAIRVA). Hum Vaccin 2011;7(8):845–8.
[29] Pavia-Ruz N, Angel Rodriguez Weber M, Lau YL, Nelson EA, Kerdpanich A, Huang LM, et al. A randomized controlled study to evaluate the immunogenicity of a trivalent inactivated seasonal influenza vaccine at two dosages in children 6 to 35 months of age. Hum Vaccin Immunother 2013;9(9):1978–88.
[30] Vesikari T, Groth N, Karvonen A, Borkowski A, Pellegrini M. MF59-adjuvanted influenza vaccine (FLUAD) in children: safety and immunogenicity following a second year seasonal vaccination. Vaccine 2009;27(45):6291–5.
[31] Vesikari T, Block SL, Guerra F, Lattanzi M, Holmes S, Izu A, et al. Immunogenicity, safety and reactogenicity of a mammalian cell-culture-derived influenza vaccine in healthy children and adolescents three to seventeen years of age. Pediatr Infect Dis J 2012;31(5):494–500.
[32] Durando P, Icardi G, Ansaldi F. MF59-adjuvanted vaccine: a safe and useful tool to enhance and broaden protection against seasonal influenza viruses in subjects at risk. Expert Opin Biol Ther 2010;10(4):639–51.
[33] Jackson LA, Chen WH, Stapleton JT, Dekker CL, Wald A, Brady RC, et al. Immunogenicity and safety of varying dosages of a monovalent 2009 H1N1 influenza vaccine given with and without AS03 adjuvant system in healthy adults and older persons. J Infect Dis 2012;206(6):811–20.
[34] Law B, Lafleche J. Cellulitis reported to the Canadian adverse events following immunization surveillance system (1987–2012). Pharmacoepidemiol Drug Saf 2013;22(Suppl. 1):255–6.
[35] Burwen DR, La Voie L, Braun MM, Houck P, Ball R. Evaluating adverse events after vaccination in the Medicare population. Pharmacoepidemiol Drug Saf 2007;16(7):753–61.
[36] Owensby JE, Elliott S, Tu K, Hernandez JE. Cellulitis and myositis caused by Agrobacterium radiobacter and Haemophilus parainfluenzae after influenza virus vaccination. South Med J 1997;90(7):752–4.
[37] Ben-Shoshan M, Lejtenyi C, Primeau MN. The predilection of chickenpox exanthema to influenza vaccine injection site. Pediatr Dermatol 2009;26(4):481–2.
[38] Demoly P, Tanno LK, Akdis CA, Lau S, Calderon MA, Santos AF, et al. Global classification and coding of hypersensitivity diseases – an EAACI – WAO survey, strategic paper and review. Allergy 2014;69(5):559–70.
[39] Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò MB, et al. Management of anaphylaxis: a systematic review. Allergy 2014;69(2):168–75.
[40] Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J 2014;7(1):9.
[41] Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med 2012;18(5):693–704.
[42] Commins SP, Platts-Mills TA. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). Curr Allergy Asthma Rep 2013;13(1):72–7.
[43] Wood RA. Allergic reactions to vaccines. Pediatr Allergy Immunol 2013;24(6):521–6.
[44] Kelso JM. Administering influenza vaccine to egg-allergic persons. Expert Rev Vaccines 2014;13(8):1049–57.
[45] Institute for Vaccine Safety. Allergens table; 2013. Available at http://vaccinesafety.edu/components-Allergens.htm.
[46] Smith CC. Risk of latex allergy from medication vial closures. Ann Pharmacother 1999;33(3):373–4.
[47] Mark C. Large variations in the ovalbumin content in six European influenza vaccines. Pharmeur Sci Notes 2006;2006(1):27–9.
[48] McKinney KK, Webb L, Petersen M, Nelson M, Laubach S. Ovalbumin content of 2010–2011 influenza vaccines. J Allergy Clin Immunol 2011;127(6):1629–32.
[49] Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012;130:25–43.
[50] Grohskopf LA, Olsen SJ, Sokolow LZ, Bresee JS, Cox NJ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2014–15 influenza season. Morb Mortal Wkly Rep 2014;63(32):691–7.
[51] Owens G, MacGinnitie A. Higher-ovalbumin-content influenza vaccines are well tolerated in children with egg allergy. J Allergy Clin Immunol 2011;127:264–5.
[52] Rouleau I, De Serres G, Skowronski DM, Drolet JP, Lemire C, Toth E, et al. Risk factors associated with anaphylaxis and other allergic-like events following receipt of 2009 monovalent AS03-adjuvanted pandemic influenza vaccine in Quebec, Canada. Vaccine 2014;32(28):3480–7.
[53] Seitz CS, Bröcker EB, Trautmann A. Vaccination-associated anaphylaxis in adults: diagnostic testing ruling out IgE-mediated vaccine allergy. Vaccine 2009;27(29):3885–9.
[54] Rouleau I, De Serres G, Drolet JP, Banerjee D, Lemire C, Moore A, et al. Allergic symptoms after pandemic influenza vaccination rarely mediated by vaccine-specific IgE. J Allergy Clin Immunol 2012;130(6):1423–6.
[55] Bonds RS, Kelly BC. Severe serum sickness after H1N1 influenza vaccination. Am J Med Sci 2013;345(5):412–3.

[56] Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol 2002;110(3):341–8.
[57] De Serres G, Grenier JL, Toth E, Ménard S, Roussel R, Tremblay M, et al. The clinical spectrum of the oculo-respiratory syndrome after influenza vaccination. Vaccine 2003;21(19–20):2354–61.
[58] De Serres G, Toth E, Ménard S, Grenier JL, Roussel R, Tremblay M, et al. Oculo-respiratory syndrome after influenza vaccination: trends over four influenza seasons. Vaccine 2005;23(28):3726–32.
[59] Babiuk S, Skowronski DM, De Serres G, HayGlass K, Brunham RC, Babiuk L. Aggregate content influences the Th1/Th2 immune response to influenza vaccine: evidence from a mouse model. J Med Virol 2004;72(1):138–42.
[60] Skowronski DM, Bjornson G, Husain E, Metzger DL, Scheifele DW. Oculorespiratory syndrome after influenza immunization in children. Pediatr Infect Dis J 2005;24(1):63–9.
[61] National Advisory Committee on Immunization (NACI), An Advisory Committee Statement (ACS), National Advisory Committee on Immunization (NACI). Supplementary Statement for the 2001–2002 season: influenza vaccination of persons who experienced oculo-respiratory syndrome following previous influenza vaccination. Can Commun Dis Rep 2001;27:1–7.
[62] Halsey NA, Griffioen M, Dreskin SC, Dekker CL, Wood R, Sharma D, et al. Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS. Vaccine 2013;31(51):6107–12.
[63] National Advisory Committee on Immunization (NACI). Statement on influenza vaccination for the 2003–2004 season. Can Commun Dis Rep 2003;29:1–20.
[64] van der Tweel I, Askie L, Vandermeer B, Ellenberg S, Fernandes RM, Saloojee H, et al. Standard 4: determining adequate sample sizes. Pediatrics 2012;129(Suppl. 3):S138–45.
[65] Lieberman JA, Sicherer SH. Diagnosis of food allergy: epicutaneous skin tests, in vitro tests, and oral food challenge. Curr Allergy Asthma Rep 2011;11(1):58–64.
[66] Englund JA, Walter E, Black S, Blatter M, Nyberg J, Ruben FL, et al. Safety and immunogenicity of trivalent inactivated influenza vaccine in infants: a randomized double-blind placebo-controlled study. Pediatr Infect Dis J 2010;29(2):105–10.
[67] Mahajan D, Roomiani I, Gold MS, Lawrence GL, McIntyre PB, Menzies RI. Annual report: surveillance of adverse events following immunisation in Australia, 2009. Commun Dis Intell Q Rep 2010;34(3):259–76.
[68] Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25(31):5675–84.
[69] Vidal P, Reyna J, Saldaña P, Richardson VL. Events temporarily associated with anti-influenza A (H1N1) vaccination in Mexico. Arch Med Res 2011;42(7):627–32.
[70] Banzhoff A, Haertel S, Praus M. Passive surveillance of adverse events of an MF59-adjuvanted H1N1v vaccine during the pandemic mass vaccinations. Hum Vaccin 2011;7(5):539–48.
[71] Tavares F, Delaigle A, Slavin D, Bauchau V, Fries L, Seifert H. Anaphylaxis following H1N1 pandemic vaccines: safety data in perspective. Vaccine 2011;29(37):6402–7.
[72] Rouleau I, De Serres G, Drolet JP, Skowronski DM, Ouakki M, Toth E, et al. Increased risk of anaphylaxis following administration of 2009 AS03-adjuvanted monovalent pandemic A/H1N1 (H1N1pdm09) vaccine. Vaccine 2013;31(50):5989–96.
[73] Kim JH, Cho HY, Hennessey KA, Lee HJ, Bae GR, Kim HC. Adverse events following immunization (AEFI) with the novel influenza a (H1N1) 2009 vaccine: findings from the national registry of all vaccine recipients and AEFI and the passive surveillance system in South Korea. Jpn J Infect Dis 2012;65(2):99–104.
[74] Izurieta HS, Haber P, Wise RP, Iskander J, Pratt D, Mink C, et al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. JAMA 2005;294(21):2720–5.
[75] Domingues E, Sweeney SM, Belazarian L. Gianotti-Crosti syndrome in a child following intranasal influenza virus vaccination. Eur J Pediatr Dermatol 2009;19(3):143–5.
[76] Liu PY, Shi ZY, Lee CH. Cutaneous vasculitis following influenza vaccination. Intern Med 2010;49(19):2187–8.
[77] Iwane MK, Prill MM, Lu X, Miller EK, Edwards KM, Hall CB, et al. Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. J Infect Dis 2011;204(11):1702–10.
[78] Watanabe T. Henoch-Schönlein purpura following influenza vaccinations during the pandemic of influenza A (H1N1). Pediatr Nephrol 2011;26(5):795–8.
[79] Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22(5–6):551–6.
[80] Barry DW, Mayner RE, Hochstein HD, Dunlap RC, Rastogi SC, Hannah JE, et al. Comparative trial of influenza vaccines, II. Adverse reactions in children and adults. Am J Epidemiol 1976;104(1):47–59.
[81] Wright PF, Sell SH, Thompson J, Karzon DT. Clinical reactions and serologic response following inactivated monovalent influenza type B vaccine in young children and infants. J Pediatr 1976;88(1):31–5.
[82] Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010;126(1):e1–8.
[83] Marine WM, Stuart-Harris C. Reactions and serologic responses in young children and infants after administration of inactivated monovalent influenza A vaccine. J Pediatr 1976;88(1):26–30.
[84] Parkman PD, Hopps HE, Rastogi SC, Meyer Jr HM. Summary of clinical trials of influenza virus vaccines in adults. J Infect Dis 1977;136(Suppl):S722–30.
[85] Wright PF, Ross KB, Thompson J, Karzon DT. Influenza A infections in young children. Primary natural infection and protective efficacy of live-vaccine-induced or naturally acquired immunity. N Engl J Med 1977;296(15):829–34.
[86] Wright PF, Vaughn WK, Thompson J, Sell SH, Karzon DT. Inactivated influenza A/New Jersey/76 vaccines in children: results of a mult-center trial. Dev Biol Stand 1977;39:309–13.
[87] Gonzalez M, Pirez MC, Ward E, Dibarboure H, García A, Picolet H. Safety and immunogenicity of a paediatric presentation of an influenza vaccine. Arch Dis Child 2000;83(6):488–91.
[88] Bernstein DI, Zahradnik JM, DeAngelis CJ, Cherry JD. Clinical reactions and serologic responses after vaccination with whole-virus or split-virus influenza vaccines in children aged 6 to 36 months. Pediatrics 1982;69(4):404–8.
[89] Public Health Service (PHS) Advisory Committee on Immunization Practices, Center for Disease Control, US Department of Health, Education, and Welfare; Atlanta, Georgia. Influenza vaccine: recommendations. Ann Intern Med 1977;87(3):316–8.
[90] Delore V, Salamand C, Marsh G, Arnoux S, Pepin S, Saliou P. Long-term clinical trial safety experience with the inactivated split influenza vaccine, Vaxigrip. Vaccine 2006;24(10):1586–92.
[91] Skowronski DM, Jacobsen K, Daigneault J, Remple VP, Gagnon L, Daly P, et al. Solicited adverse events after influenza immunization among infants, toddlers, and their household contacts. Pediatrics 2006;117(6):1963–71.
[92] Englund JA, Walter EB, Fairchok MP, Monto AS, Neuzil KM. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. Pediatrics 2005;115(4):1039–47.
[93] Langley JM, Reich D, Aggarwal N, Connor D, Lebel MH, Gupta A, et al. Randomized, multicenter trial of a single dose of AS03-adjuvanted or unadjuvanted H1N1 2009 pandemic influenza vaccine in children 6 months to <9 years of age: safety and immunogenicity. Pediatr Infect Dis J 2012;31(8):848–58.
[94] Langley JM, Scheifele DW, Quach C, Vanderkooi OG, Ward B, McNeil S, et al. Safety and immunogenicity of 2010–2011 H1N12009-containing trivalent inactivated influenza vaccine in children 12–59 months of age previously given AS03-adjuvanted H1N12009 pandemic vaccine: a PHAC/CIHR Influenza Research Network (PCIRN) study. Vaccine 2012;30(23):3389–94.
[95] Baxter R, Jeanfreau R, Block SL, Blatter M, Pichichero M, Jain VK, et al. evaluation of immunogenicity and safety of two trivalent inactivated seasonal influenza vaccines in US children. Pediatr Infect Dis J 2010;29(10):924–30.
[96] Langley JM, Carmona Martinez A, Chatterjee A, Halperin SA, McNeil S, Reisinger KS, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate: a phase III randomized controlled trial in children. J Infect Dis 2013;208(4):544–53.
[97] Domachowske JB, Pankow-Culot H, Bautista M, Feng Y, Claeys C, Peeters M, et al. A randomized trial of candidate inactivated quadrivalent influenza vaccine versus trivalent influenza vaccines in children aged 3–17 years. J Infect Dis 2013;207(12):1878–87.
[98] Greenberg DP, Robertson CA, Landolfi VA, Bhaumik A, Senders SD, Decker MD. Safety and immunogenicity of an inactivated quadrivalent influenza vaccine in children 6 months through 8 years of age. Pediatr Infect Dis J 2014;33(6):630–6.
[99] Zhu FC, Wang H, Fang HH, Yang JG, Lin XJ, Liang XF, et al. A novel influenza A (H1N1) vaccine in various age groups. N Engl J Med 2009;361(25):2414–23.
[100] Nolan T, Richmond PC, Formica NT, Höschler K, Skeljo MV, Stoney T, et al. Safety and immunogenicity of a prototype adjuvanted inactivated split-virus influenza A (H5N1) vaccine in infants and children. Vaccine 2008;26(50):6383–91.
[101] Carmona A, Omeñaca F, Tejedor JC, Merino JM, Vaman T, Dieussaert I, et al. Immunogenicity and safety of AS03-adjuvanted 2009 influenza A H1N1 vaccine in children 6–35 months. Vaccine 2010;28(36):5837–44.
[102] Launay O, Duval X, Fitoussi S, Jilg W, Kerdpanich A, Montellano M, et al. Extended antigen sparing potential of AS03-adjuvanted pandemic H1N1 vaccines in children, and immunological equivalence of two formulations of AS03-adjuvanted H1N1 vaccines: results from two randomised trials. BMC Infect Dis 2013;13:435.
[103] Poder A, Simurka P, Li P, Roy-Ghanta S, Vaughn D. An observer-blind, randomized, multi-center trial assessing long-term safety and immunogenicity of AS03-adjuvanted or unadjuvanted H1N1/2009 influenza vaccines in children 10–17 years of age. Vaccine 2014;32(9):1121–9.
[104] Pellegrini M, Nicolay U, Lindert K, Groth N, Della Cioppa G. MF59-adjuvanted versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database. Vaccine 2009;27(49):6959–65.
[105] Black S, Della Cioppa G, Malfroot A, Nacci P, Nicolay U, Pellegrini M, et al. Safety of MF59-adjuvanted versus non-adjuvanted influenza vaccines in children and adolescents: an integrated analysis. Vaccine 2010;28(45):7331–6.
[106] Esposito S, Pugni L, Daleno C, Ronchi A, Valzano A, Serra D, et al. Influenza A/H1N1 MF59-adjuvanted vaccine in preterm and term children aged 6 to 23 months. Pediatrics 2011;127(5):e1161–8.
[107] Block SL, Falloon J, Hirschfield JA, Krilov LR, Dubovsky F, Yi T, et al. Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. Pediatr Infect Dis J 2012;31(7):745–51.

[108] Knuf M, Leroux-Roels G, Rümke HC, Abarca K, Rivera L, Lattanzi M, et al. Immunogenicity and tolerability of an MF59-adjuvanted, egg-derived. A/H1N1 pandemic influenza vaccine in children 6–35 months of age. Pediatr Infect Dis J 2014;33(12):e320–9.
[109] Nolan T, Bravo L, Ceballos A, Mitha E, Gray G, Quiambao B, et al. Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children. Vaccine 2014;32(46):6146–56.
[110] Stockwell MS, Broder K, LaRussa P, Lewis P, Fernandez N, Sharma D, et al. Risk of fever after pediatric trivalent inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine. JAMA Pediatr 2014;168(3):211–9.
[111] American Academy of Pediatrics (AAP); Subcommittee on Febrile Seizures. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 2008;121(6):1281–6.
[112] American Academy of Pediatrics (AAP); Subcommittee on Febrile Seizures. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 2011;127(2):389–94.
[113] Teng D, Dayan P, Tyler S, Hauser WA, Chan S, Leary L, et al. Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. Pediatrics 2006;117(2):304–8.
[114] Mewasingh LD. Febrile seizures. Clin Evid (Online) 2014:2014.
[115] Vestergaard M, Christensen J. Register-based studies on febrile seizures in Denmark. Brain Dev 2009;31(5):372–7.
[116] Saghazadeh A, Mastrangelo M, Rezaei N. Genetic background of febrile seizures. Rev Neurosci 2014;25(1):129–61.
[117] Principi N, Esposito S. Vaccines and febrile seizures. Expert Rev Vaccines 2013;12(8):885–92.
[118] Verbeek NE, Jansen FE, Vermeer-de Bondt PE, de Kovel CG, van Kempen MJ, Lindhout D, et al. Etiologies for seizures around the time of vaccination. Pediatrics 2014;134(4):658–66.
[119] Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004;22(5–6):557–62.
[120] McMahon AW, Iskander J, Haber P, Chang S, Woo EJ, Braun MM, et al. Adverse events after inactivated influenza vaccination among children less than 2 years of age: analysis of reports from the vaccine adverse event reporting system, 1990–2003. Pediatrics 2005;115(2):453–60.
[121] Rosenberg M, Sparks R, McMahon A, Iskander J, Campbell JD, Edwards KM. Serious adverse events rarely reported after trivalent inactivated influenza vaccine (TIV) in children 6–23 months of age. Vaccine 2009;27(32):4278–83.
[122] Muhammad RD, Haber P, Broder KR, Leroy Z, Ball R, Braun MM, et al. Adverse events following trivalent inactivated influenza vaccination in children: analysis of the vaccine adverse event reporting system. Pediatr Infect Dis J 2011;30(1):e1–8.
[123] France EK, Glanz JM, Xu S, Davis RL, Black SB, Shinefield HR, et al. Safety of the trivalent inactivated influenza vaccine among children: a population-based study. Arch Pediatr Adolesc Med 2004;158(11):1031–6.
[124] Hambidge SJ, Glanz JM, France EK, McClure D, Xu S, Yamasaki K, et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA 2006;296(16):1990–7.
[125] Goodman MJ, Nordin JD, Harper P, DeFor T, Zhou X. The safety of trivalent influenza vaccine among healthy children 6 to 24 months of age. Pediatrics 2006;117(5):e821–6.
[126] Glanz JM, Newcomer SR, Hambidge SJ, Daley MF, Narwaney KJ, Xu S, et al. Safety of trivalent inactivated influenza vaccine in children aged 24 to 59 months in the vaccine safety datalink. Arch Pediatr Adolesc Med 2011;165(8):749–55.
[127] Nazareth I, Tavares F, Rosillon D, Haguinet F, Bauchau V. Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study. BMJ Open 2013;3(2).
[128] Armstrong PK, Dowse GK, Effler PV, Carcione D, Blyth CC, Richmond PC, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. BMJ Open 2011;1(1):e000016.
[129] Mahajan D, Cook J, McIntyre PB, Macartney K, Menzies RI. Annual report: surveillance of adverse events following immunisation in Australia, 2010. Commun Dis Intell Q Rep 2011;35(4):263–80.
[130] Wood N, Sheppeard V, Cashman P, Palasanthiran P, Casacelli M, Cannings K, et al. Influenza vaccine safety in children less than 5 years old: the 2010 and 2011 experience in Australia. Pediatr Infect Dis J 2012;31(2):199–202.
[131] Salisbury DM. Letter to general practitioners; 2010. Available at: https://www.gov.uk/government/publications/seasonal-flu-immunisation-programme-2011-12.
[132] Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, et al. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine in infants and children: a randomized trial. JAMA 2010;303(1):37–46.
[133] Cook J. Australian experience with non-adjuvant H1N1 vaccine (Panvax and Panvax Junior). Aust Prescr 2010;33(4):121–3.
[134] Lambert SB, Chuk LMR, Nissen MD, Nolan TM, McVernon J, Booy R, et al. Safety and tolerability of a 2009 trivalent inactivated split-virion influenza vaccine in infants, children and adolescents. Influenza Other Respir Viruses 2013;7(5):676–85.
[135] Nolan T, Richmond PC, McVernon J, Skeljo MV, Hartel GF, Bennet J, et al. Safety and immunogenicity of an inactivated thimerosal-free influenza vaccine in infants and children. Influenza Other Respir Viruses 2009;3(6):315–25.
[136] Petousis-Harris H, Poole T, Booy R, Turner N. Fever following administration of two inactivated influenza vaccines-A survey of parents of New Zealand infants and children 5 years of age and under. Vaccine 2011;29(16):2933–7.
[137] Kaczmarek MC, Duong UT, Ware RS, Lambert SB, Kelly HA. The risk of fever following one dose of trivalent inactivated influenza vaccine in children aged (greater-than or equal to)6 months to <36 months: a comparison of published and unpublished studies. Vaccine 2013;31(46):5359–65.
[138] Maraskovsky E, Rockman S, Dyson A, Koernig S, Becher D, Morelli AB, et al. Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine. Vaccine 2012;30(51):7400–6.
[139] Rockman S, Becher D, Dyson A, Koernig S, Morelli AB, Barnden M, et al. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. Vaccine 2014;32(30):3869–76.
[140] Rockman S, Dyson A, Koernig S, Becher D, Ng M, Morelli AB, et al. Evaluation of the bioactivity of influenza vaccine strains in vitro suggests that the introduction of new strains in the 2010 Southern Hemisphere trivalent influenza vaccine is associated with adverse events. Vaccine 2014;32(30):3861–8.
[141] World Health Organization. Global Advisory Committee on Vaccine Safety, 11–12 December 2013. Wkly Epidemiol Rec 2014;89(7):53–60.
[142] Kelly HA, Skowronski DM, de Serres G, Effler PV. Adverse events associated with 2010 CSL and other inactivated influenza vaccines. Med J Aust 2011;195(6):318–20.
[143] Liang XF, Li L, Liu DW, Li KL, Wu WD, Zhu BP, et al. Safety of influenza A (H1N1) vaccine in postmarketing surveillance in China. N Engl J Med 2011;364(7):638–47.
[144] Folkenberg M, Callreus T, Svanstrom H, Valentiner-Branth P, Hviid A. Spontaneous reporting of adverse events following immunisation against pandemic influenza in Denmark November 2009–March 2010. Vaccine 2011;29(6):1180–4.
[145] Kraigher A, Ucakar V. Surveillance of adverse events following immunization against pandemic influenza in Slovenia in season 2009/10. Vaccine 2010;28(33):5467–72.
[146] van Puijenbroek EP, Broos N, van Grootheest K. Monitoring adverse events of the vaccination campaign against influenza A (H1N1) in the Netherlands. Drug Saf 2010;33(12):1097–108.
[147] 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;29(51):9467–72.
[148] Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010–2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. Vaccine 2012;30(11):2020–3.
[149] Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011. Vaccine 2012;30(11):2024–31.
[150] Tse AC, Tseng HF, Greene SK, Vellozzi C, Weintraub E, McCarthy N, et al. Risk of febrile seizures in children following trivalent inactivated influenza vaccine in the vaccine safety datalink project, 2010–2011. Pharmacoepidemiol Drug Saf 2012;21:365–6.
[151] Duffy J. Seizures following administration of multiple vaccines: a VSD study. In: Slide presentation at: meeting of the Advisory Committee on Immunization Practices (ACIP). 2014.
[152] Kawai AT, Li L, Kulldorff M, Vellozzi C, Weintraub E, Baxter R, et al. Absence of associations between influenza vaccines and increased risks of seizures. Guillain-Barré syndrome, encephalitis, or anaphylaxis in the 2012–2013 season. Pharmacoepidemiol Drug Saf 2014;23(5):548–53.
[153] Van Buynder PG, Frosst G, Van Buynder JL, Tremblay FW, Ross A, Jardine C, et al. Increased reactions to pediatric influenza vaccination following concomitant pneumococcal vaccination. Influenza Other Respir Viruses 2013;7(2):184–90.
[154] Lum LC, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine 2010;28(6):1566–74.
[155] Reynales H, Astudillo P, de Valliere S, Hatz C, Schlagenhauf P, Rath B, et al. A prospective observational safety study on MF59 (registered trademark) adjuvanted cell culture-derived vaccine. Celtura(registered trademark) during the A/H1N1 (2009) influenza pandemic. Vaccine 2012;30(45):6436–43.
[156] Haber P, Moro PL, McNeil MM, Lewis P, Woo EJ, Hughes H, et al. Post-licensure surveillance of trivalent live attenuated influenza vaccine in adults, United States, Vaccine Adverse Event Reporting System (VAERS), July 2005–June 2013. Vaccine 2014;32(48):6499–504.
[157] FluMist® Quadrivalent. (Influenza vaccine live, intranasal), intranasal spray, 2014–2015 formula: package insert; 2014.
[158] Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med 2007;356(7):685–96 [Erratum in: N Engl J Med 2007;356(12):1283].
[159] Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine 2011;29(31):4947–52.
[160] Tennis P, Toback SL, Andrews EB, McQuay LJ, Ambrose CS. A US postmarketing evaluation of the frequency and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years: 2009–2010 season. Vaccine 2012;30(42):6099–102.

[161] McElhaney JE, Beran J, Devaster JM, Esen M, Launay O, Leroux-Roels G, et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. Lancet Infect Dis 2013;13(6):485–96.

[162] World Health Organization/Global Vaccine Safety. Information sheet: observed rate of vaccine reactions – influenza vaccine; 2012. Available at: http://www.who.int/vaccine_safety/initiative/tools/Influenza_Vaccine_rates_information_sheet.pdf?ua=1 [accessed 26.05.15].

[163] Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. JAMA 1990;264(9):1139–41 [Erratum in: JAMA 1991;265(21):2810].

[164] Margolis KL, Poland GA, Nichol KL, MacPherson DS, Meyer JD, Korn JE, et al. Frequency of adverse reactions after influenza vaccination. Am J Med 1990;88(January (1)):27–30.

[165] Nichol KL, Margolis KL, Lind A, Murdoch M, McFadden R, Hauge M, et al. Side effects associated with influenza vaccination in healthy working adults. A randomized, placebo-controlled trial. Arch Intern Med 1996;156(14):1546–50.

[166] Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine 2007;25(44):7656–63.

[167] Beran J, Peeters M, Dewé W, Raupachová J, Hobzová L, Devaster JM. Immunogenicity and safety of quadrivalent versus trivalent inactivated influenza vaccine: a randomized, controlled trial in adults. BMC Infect Dis 2013;13:224.

[168] Vellozzi C, Broder KR, Haber P, Guh A, Nguyen M, Cano M, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31 2010. Vaccine 2010;28(45):7248–55.

[169] Brady RC, Hu W, Houchin VG, Eder FS, Jackson KC, Hartel GF, et al. Randomized trial to compare the safety and immunogenicity of CSL Limited's 2009 trivalent inactivated influenza vaccine to an established vaccine in United States children. Vaccine 2014;32(52):7141–7.

[170] Tregnaghi MW, Stamboulian D, Vanadía PC, Tregnaghi JP, Calvari M, Fragapane E, et al. Immunogenicity, safety, and tolerability of two trivalent subunit inactivated influenza vaccines: a phase III, observer-blind, randomized, controlled multicenter study. Viral Immunol 2012;25(3):216–25.

[171] Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Arch Intern Med 2000;160(21):3243–7.

[172] Beigel JH. Influenza. Crit Care Med 2008;36(9):2660–6.

[173] Hoek KL, Samir P, Howard LM, Niu X, Prasad N, Galassie A, et al. A cell-based systems biology assessment of human blood to monitor immune responses after influenza vaccination. PLOS ONE 2015;10(2):e0118528.

[174] Obermoser G, Presnell S, Domico K, Xu H, Wang Y, Anguiano E, et al. Systems scale interactive exploration reveals quantitative and qualitative differences in response to influenza and pneumococcal vaccines. Immunity 2013;38(4):831–44.

[175] Ramakrishnan A, Althoff KN, Lopez JA, Coles CL, Bream JH. Differential serum cytokine responses to inactivated and live attenuated seasonal influenza vaccines. Cytokine 2012;60(3):661–6.

[176] Christian LM, Iams JD, Porter K, Glaser R. Inflammatory responses to trivalent influenza virus vaccine among pregnant women. Vaccine 2011;29(48):8982–7.

[177] Christian LM, Porter K, Karlsson E, Schultz-Cherry S, Iams JD. Serum proinflammatory cytokine responses to influenza virus vaccine among women during pregnancy versus non-pregnancy. Am J Reprod Immunol 2013;70(1):45–53.

[178] Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. J Rheumatol 1995;22(8):1566–9.

[179] Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369(9563):767–78.

[180] Angeles-Han S, Prahalad S. The genetics of juvenile idiopathic arthritis: what is new in 2010? Curr Rheumatol Rep 2010;12(2):87–93.

[181] Berkun Y, Padeh S. Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. Autoimmun Rev 2010;9(5):A319–24.

[182] Aslan M, Kasapcopur O, Yasar H, Polat E, Saribas S, Cakan H, et al. Do infections trigger juvenile idiopathic arthritis? Rheumatol Int 2011;31(2):215–20.

[183] Shimizu M, Ueno K, Yachie A. Relapse of systemic juvenile idiopathic arthritis after influenza vaccination in a patient receiving tocilizumab. Clin Vaccine Immunol 2012;19(10):1700–2.

[184] Asakawa J, Kobayashi S, Kaneda K, Ogasawara H, Sugawara M, Yasuda M, et al. Reactive arthritis after influenza vaccination: report of a case. Mod Rheumatol 2005;15(4):283–5.

[185] Yoshioka K, Fujimoto S, Oba H, Minami M, Aoki T. Onset of adult-onset Still's disease following influenza vaccination. Mod Rheumatol 2011;21(4):432–5.

[186] De Nardo P, Bellagamba R, Corpolongo A, Gentilotti E, Taglietti F, Rosati S, et al. Septic shock after seasonal influenza vaccination in an HIV-infected patient during treatment with etanercept for rheumatoid arthritis: a case report. Clin Vaccine Immunol 2013;20(5):761–4.

[187] Chalmers A, Scheifele D, Patterson C, Williams D, Weber J, Shuckett R, et al. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. J Rheumatol 1994;21(7):1203–6.

[188] Harrison BJ, Thomson W, Pepper L, Ollier WE, Chakravarty K, Barrett EM, et al. Patients who develop inflammatory polyarthritis (IP) after immunization are clinically indistinguishable from other patients with IP. Br J Rheumatol 1997;36(3):366–9.

[189] Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis 2008;67(7):937–41.

[190] Aikawa NE, Campos LM, Silva CA, Carvalho JF, Saad CG, Trudes G, et al. Glucocorticoid: major factor for reduced immunogenicity of 2009 influenza A (H1N1) vaccine in patients with juvenile autoimmune rheumatic disease. J Rheumatol 2012;39(1):167–73.

[191] Toplak N, Subelj V, Kveder T, Cucnik S, Prosenc K, Trampus-Bakija A, et al. Safety and efficacy of influenza vaccination in a prospective longitudinal study of 31 children with juvenile idiopathic arthritis. Clin Exp Rheumatol 2012;30(3):436–44.

[192] Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum 2011;63(6):1486–96.

[193] Elkayam O, Amir S, Arad U, Wollman J, Brill A, Paran D, et al. The cellular response to vaccination against pandemic 2009 influenza A (H1N1) virus among patients with rheumatic diseases. Arthritis Care Res 2011;63(10 Suppl):1.

[194] Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis 2011;70(6):1068–73.

[195] Shinoki T, Hara R, Kaneko U, Miyamae T, Imagawa T, Mori M, et al. Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab. Mod Rheumatol 2012;22(6):871–6.

[196] Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15–59 years of age. Vaccine 2011;29(38):6592–7.

[197] Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ 2011;343:d5956.

[198] Baxter R, Toback SL, Sifakis F, Hansen J, Bartlett J, Aukes L, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age. Vaccine 2012;30(19):2989–98.

[199] Bengtsson C, Kapetanovic MC, Källberg H, Sverdrup B, Nordmark B, Klareskog L, et al. Common vaccinations among adults do not increase the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis 2010;69(10):1831–3.

[200] Bodor M, Montalvo E. Vaccination-related shoulder dysfunction. Vaccine 2007;25(4):585–7.

[201] Atanasoff S, Ryan T, Lightfoot R, Johann-Liang R. Shoulder injury related to vaccine administration (SIRVA). Vaccine 2010;28(51):8049–52.

[202] Okur G, Chaney KA, Lomasney LM. Magnetic resonance imaging of abnormal shoulder pain following influenza vaccination. Skelet Radiol 2014;43(9):1325–31.

[203] Barnes MG, Ledford C, Hogan K. A "needling" problem: shoulder injury related to vaccine administration. J Am Board Fam Med 2012;25(6):919–22.

[204] Shaikh MF, Baqai TJ, Tahir H. Acute brachial neuritis following influenza vaccination. BMJ Case Rep 2012.

[205] Kuether G, Dietrich B, Smith T, Peter C, Gruessner S. Atraumatic osteonecrosis of the humeral head after influenza A-(H1N1) v-2009 vaccination. Vaccine 2011;29(40):6830–3.

[206] Foster S, Davis MV. Vaccine administration: preventing serious shoulder injuries. J Am Pharm Assoc 2013;53(1):102–3.

[207] Cook IF. Subdeltoid/subacromial bursitis associated with influenza vaccination. Hum Vaccin Immunother 2014;10(3):605–6.

[208] Vucic S, Kiernan MC, Cornblath DR. Guillain-Barré syndrome: an update. J Clin Neurosci 2009;16(6):733–41.

[209] Willison HJ. The immunobiology of Guillain-Barré syndromes. J Peripher Nerv Syst 2005;10(2):94–112.

[210] Vellozzi C, Iqbal S, Broder K. Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence. Clin Infect Dis 2014;58(8):1149–55.

[211] Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC. Guillain-Barré syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. PLoS ONE 2007;2(4):e344.

[212] Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. Am J Epidemiol 2009;169(3):382–8.

[213] Rees JH, Soudain SE, Gregson NA, Hughes RA. *Campylobacter jejuni* infection and Guillain-Barré syndrome. N Engl J Med 1995;333(21):1374–9.

[214] Mizoguchi K. Anti-GQ1b IgG antibody activities related to the severity of Miller Fisher syndrome. Neurol Res 1998;20(7):617–24.

[215] Ellenberg SS, Braun MM. Monitoring the safety of vaccines: assessing the risks. Drug Saf 2002;25(3):145–52.

[216] Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol 1979;110(2):105–23.

[217] Salmon DA, Proschan M, Forshee R, Gargiullo P, Bleser W, Burwen DR, et al. Association between Guillain-Barré syndrome and influenza A (H1N1)

2009 monovalent inactivated vaccines in the USA: a meta-analysis. Lancet 2013;381(9876):1461–8.
[218] Langmuir AD. Guillain-Barré syndrome: the swine influenza virus vaccine incident in the United States of America, 1976–77: preliminary communication. J R Soc Med 1979;72(9):660–9.
[219] Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2012–13 influenza season. MMWR Morb Mortal Wkly Rep 2012;61(32):613–8.
[220] Johnson DE. Guillain-Barré syndrome in the US Army. Arch Neurol 1982;39(1):21–4.
[221] Institute of Medicine. Immunization safety review: influenza vaccines and neurological complications. Washington, DC: The National Academies Press; 2003.
[222] Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. N Engl J Med 1998;339(25):1797–802.
[223] Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med 2006;166(20):2217–21.
[224] Nachamkin I, Shadomy SV, Moran AP, Cox N, Fitzgerald C, Ung H, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. J Infect Dis 2008;198(2):226–33.
[225] Wang DJ, Boltz DA, McElhaney J, McCullers JA, Webby RJ, Webster RG. No evidence of a link between influenza vaccines and Guillain-Barre syndrome-associated antiganglioside antibodies. Influenza Other Respir Viruses 2012;6(3):159–66.
[226] Lei T, Siu KL, Kok KH, Chan KH, Chan EY, Hung IF, et al. Anti-ganglioside antibodies were not detected in human subjects infected with or vaccinated against 2009 pandemic influenza A (H1N1) virus. Vaccine 2012;30(16):2605–10.
[227] Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011;29(3):599–612.
[228] Sejvar JJ, Pfeifer D, Schonberger LB. Guillain-barré syndrome following influenza vaccination: causal or coincidental? Curr Infect Dis Rep 2011;13(4):387–98.
[229] Brostoff SW, White TM. Absence of P2 protein in swine flu vaccines. JAMA 1982;247(4):495.
[230] Hjorth RN, Bonde GM, Piner E, Hartzell RW, Rorke LB, Rubin BA. Experimental neuritis induced by a mixture of neural antigens and influenza vaccines. A possible model for Guillain-Barré syndrome. J Neuroimmunol 1984;6(1):1–8.
[231] Kramarz P, DeStefano F, Gargiullo PM, Davis RL, Chen RT, Mullooly JP, et al. Does influenza vaccination exacerbate asthma? Analysis of a large cohort of children with asthma. Vaccine Safety Datalink Team. Arch Fam Med 2000;9(7):617–23.
[232] Burwen DR, Sandhu SK, MaCurdy TE, Kelman JA, Gibbs JM, Garcia B, et al. Surveillance for Guillain-Barré syndrome after influenza vaccination among the Medicare population, 2009–2010. Am J Public Health 2012;102(10):1921–7.
[233] Greene SK, Rett M, Weintraub ES, Li L, Yin R, Amato AA, et al. Risk of confirmed Guillain-Barre syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink Project, 2009–2010. Am J Epidemiol 2012;175(11):1100–9.
[234] Polakowski LL, Sandhu SK, Martin DB, Ball R, Macurdy TE, Franks RL, et al. Chart-confirmed guillain-barre syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009–2010. Am J Epidemiol 2013;178(6):962–73.
[235] Tokars JI, Lewis P, DeStefano F, Wise M, Viray M, Morgan O, et al. 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;21(5):546–52.
[236] Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006;25(10):1768–97.
[237] Carr S, Allison KJ, Van De Velde LA, Zhang K, English EY, Iverson A, et al. Safety and immunogenicity of live attenuated and inactivated influenza vaccines in children with cancer. J Infect Dis 2011;204(10):1475–82.
[238] CDC. Preliminary results: surveillance for Guillain-Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine – United States, 2009–2010. Morb Mortal Wkly Rep 2010;59(21):657–61.
[239] Dodd CN, Romio SA, Black S, Vellozzi C, Andrews N, Sturkenboom M, et al. International collaboration to assess the risk of Guillain Barré syndrome following influenza A (H1N1) 2009 monovalent vaccines. Vaccine 2013;31(40):4448–58.
[240] Prestel J, Volkers P, Mentzer D, Lehmann HC, Hartung HP, Keller-Stanislawski B, et al. Risk of Guillain-Barré syndrome following pandemic influenza A(H1N1) 2009 vaccination in Germany. Pharmacoepidemiol Drug Saf 2014;23(11):1192–204.
[241] Huang WT, Yang HW, Liao TL, Wu WJ, Yang SE, Chih YC, et al. Safety of pandemic (H1N1) 2009 monovalent vaccines in taiwan: a self-controlled case series study. PLOS ONE 2013;8(3):e58827.
[242] Galeotti F, Massari M, D'Alessandro R, Beghi E, Chiò A, Logroscino G, et al. Risk of Guillain-Barré syndrome after 2010–2011 influenza vaccination. Eur J Epidemiol 2013;28(5):433–44.
[243] Greene SK, Rett MD, Vellozzi C, Li L, Kulldorff M, Marcy SM, et al. Guillain-Barré syndrome, influenza vaccination, and antecedent respiratory and gastrointestinal infections: a case-centered analysis in the Vaccine Safety Datalink, 2009–2011. PLOS ONE 2013;8(6):e67185.
[244] Kwong JC, Vasa PP, Campitelli MA, Hawken S, Wilson K, Rosella LC, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study. Lancet Infect Dis 2013;13(9):769–76.
[245] Reik Jr L. Neurological complications of immunization. Neurol Infect Epidemiol 1997;2(2):69–98.
[246] Ekstrand JJ. Neurologic complications of influenza. Semin Pediatr Neurol 2012;19(3):96–100.
[247] Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25(31):5771–92.
[248] Behan PO. Acute disseminated encephalomyelitis: postinfectious, postimmunization and variant forms. Expert Rev Neurother 2009;9(9):1321–9.
[249] Huynh W, Cordato DJ, Kehdi E, Masters LT, Dedousis C. Post-vaccination encephalomyelitis: literature review and illustrative case. J Clin Neurosci 2008;15(12):1315–22.
[250] Marchioni E, Tavazzi E, Minoli L, Del Bue S, Ferrante P, Piccolo G, et al. Acute disseminated encephalomyelitis. Neurol Sci 2008;29(Suppl. 2):S286–8.
[251] Mihai C, Jubelt B. Post-infectious encephalomyelitis. Curr Neurol Neurosci Rep 2005;5(6):440–5.
[252] Ekmekc Di, Gencer M, Tutkavul K, Varlibas F, Tireli H. Acute disseminated encephalomyelitis after H1N1 infection. Neurology 2010;17(Suppl. 3):504.
[253] Hemachudha T, Griffin DE, Giffels JJ, Johnson RT, Moser AB, Phanuphak P. Myelin basic protein as an encephalitogen in encephalomyelitis and polyneuritis following rabies vaccination. N Engl J Med 1987;316(7):369–74.
[254] Lane JM, Millar JD. Routine childhood vaccination against smallpox reconsidered. N Engl J Med 1969;281(22):1220–4.
[255] Hoshino T, Uchiyama Y, Ito E, Osawa S, Ohashi T. Simultaneous development of acute disseminated encephalomyelitis and Guillain-Barré syndrome associated with H1N1 09 influenza vaccination. Intern Med 2012;51(12):1595–8.
[256] Hopkins SE, Tillema JM, DeGrauw T. Variability in infectious disease testing for patients with acute disseminated encephalomyelitis. Ann Neurol 2010;68(Suppl. 14):S122.
[257] Masoodi I, Farooq O, Ahmad I, Bhat MY, Ahmad N, Wani HU, et al. Acute disseminated encephalomyelitis as the first presentation of CNS tuberculosis: report of a case with brief review. German Med Sci 2010;8:Doc32.
[258] Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med 2014;275(2):172–90.
[259] Isai A, Durand J, Le Meur S, Hidalgo-Simon A, Kurz X. Autoimmune disorders after immunisation with Influenza A/H1N1 vaccines with and without adjuvant: EudraVigilance data and literature review. Vaccine 2012;30(49):7123–9.
[260] Sauve LJ, Bettinger J, Vaudry W, Moore D, Scheifele D, Halperin S, et al. IMPACT network active surveillance for adverse events following adjuvanted pandemic influenza vaccine in Canadian children. Can J Infect Dis Med Microbiol 2010;21(4):180.
[261] Sacheli A, Bauer R. Influenza vaccine-induced CNS demyelination in a 50-year-old male. Am J Case Rep 2014;15:368–73.
[262] Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, et al. Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004–2009. Vaccine 2011;29(40):6920–7.
[263] Williams SE, Pahud BA, Vellozzi C, Donofrio PD, Dekker CL, Halsey N, et al. Causality assessment of serious neurologic adverse events following 2009 H1N1 vaccination. Vaccine 2011;29(46):8302–8.
[264] Pena JA, Lotze TE. Pediatric multiple sclerosis: current concepts and consensus definitions. Autoimmune Dis 2013;2013:673947.
[265] Sundqvist E, Sundström P, Lindén M, Hedström AK, Aloisi F, Hillert J, et al. Epstein-Barr virus and multiple sclerosis: interaction with HLA. Genes Immun 2012;(1):14–20.
[266] DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol 2003;60(4):504–9.
[267] Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology 2004;63(5):838–42.
[268] Ramagopalan SV, Valdar W, Dyment DA, DeLuca GC, Yee IM, Giovannoni G, et al. Association of infectious mononucleosis with multiple sclerosis. A population-based study. Neuroepidemiology 2009;32(4):257–62.
[269] Zorzon M, Zivadinov R, Nasuelli D, Dolfini P, Bosco A, Bratina A, et al. Risk factors of multiple sclerosis: a case–control study. Neurol Sci 2003;24(4):242–7.
[270] Ho TY, Huang KY, Huang TT, Huang YS, Ho HC, Chou P, et al. The impact of influenza vaccinations on the adverse effects and hospitalization rate in the elderly: a national based study in an Asian country. PLoS ONE 2012;7(11):e50337.
[271] Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. J Neurol 2011;258(7):1197–206.
[272] Miller AE, Morgante LA, Buchwald LY, Nutile SM, Coyle PK, Krupp LB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology 1997;48(2):312–4.

[273] Confavreux C, Suissa S, Saddier P, Bourdès V, Vukusic S, Vaccines in Multiple Sclerosis Study Group. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. N Engl J Med 2001;344(5):319–26.
[274] Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. Mult Scler 1997;3(4):243–7.
[275] Myers LW, Ellison GW, Lucia M, Novom S, Holevoet M, Madden D, et al. Swine influenza virus vaccination in patients with multiple sclerosis. J Infect Dis 1977;136(Suppl):S546–54.
[276] Bamford CR, Sibley WA, Laguna JF. Swine influenza vaccination in patients with multiple sclerosis. Arch Neurol 1978;35(4):242–3.
[277] Auriel E, Gaoth A, Regev K, Karni A. Seasonal and H1N1 v influenza vaccines in MS: safety and compliance. J Neuro Sci 2012;314:102–3.
[278] McNicholas N, Chataway J. Relapse risk in patients with multiple sclerosis after H1N1 vaccination, with or without seasonal influenza vaccination. J Neurol 2011;258(8):1545–7.
[279] Partinen M, Kornum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet Neurol 2014;13(6):600–13.
[280] Poli F, Overeem S, Lammers GJ, Plazzi G, Lecendreux M, Bassetti CL, et al. Narcolepsy as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. Vaccine 2013;31(6):994–1007.
[281] Ahmed SS, Schur PH, MacDonald NE, Steinman L. Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants. J Autoimmun 2014;50:1–11.
[282] Masoudi S, Ploen D, Kunz K, Hildt E. The adjuvant component α-tocopherol triggers via modulation of Nrf2 the expression and turnover of hypocretin in vitro and its implication to the development of narcolepsy. Vaccine 2014;32(25):2980–8.
[283] Johansen K. The roles of influenza virus antigens and the AS03 adjuvant in the 2009 pandemic vaccine associated with narcolepsy needs further investigation. Dev Med Child Neurol 2014;56(11):1041–2.
[284] Durrieu G, Caillet A, Faucher A, Jacquet A, Ouaret S, Auriche P, et al. Safety surveillance of influenza A(H1N1)v monovalent vaccines during the 2009–2010 mass vaccination campaign in France. Fundamental and Clinical Pharmacology 2011. Societe Francaise de Pharmacologie et de Therapeutique 2011;25(Suppl. 1):72.
[285] Partinen M. Increased incidence of narcolepsy after the A/H1N1 pandemic influenza vaccination campaign in the Nordic countries. J Sleep Res 2012;21(Suppl. 1):83.
[286] Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS ONE 2012;7(3):e33536.
[287] National Institute for Health and Welfare. Increased risk of narcolepsy observed also among adults vaccinated with Pandemrix in Finland; 2013. http://www.thl.fi/en_US/web/en/pressrelease?id=33516 [accessed 28.05.13].
[288] European Centre for Disease Prevention and Control. Narcolepsy in association with pandemic influenza vaccination (a multi-county European epidemiological investigation). Stockholm: ECDC; 2012.
[289] Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine 2013;31(8):1246–54.
[290] Tsai TF, Crucitti A, Nacci P, Nicolay U, Della Cioppa G, Ferguson J, et al. Explorations of clinical trials and pharmacovigilance databases of MF59®-adjuvanted influenza vaccines for associated cases of narcolepsy. Scand J Infect Dis 2011;43(9):702–6.
[291] McCarthy NL, Gee J, Lin ND, Thyagarajan V, Pan Y, Su S, et al. Evaluating the safety of influenza vaccine using a claims-based health system. Vaccine 2013;31(50):5975–82.
[292] Duffy J, Weintraub E, Vellozzi C, DeStefano F, Vaccine Safety Datalink. Narcolepsy and influenza A(H1N1) pandemic 2009 vaccination in the United States. Neurology 2014;83(20):1823–30.
[293] Han F. Sleepiness that cannot be overcome: narcolepsy and cataplexy. Respirology 2012;17(8):1157–65.
[294] Melén K, Partinen M, Tynell J, Sillanpää M, Himanen SL, Saarenpää-Heikkilä O, et al. No serological evidence of influenza A H1N1pdm09 virus infection as a contributing factor in childhood narcolepsy after Pandemrix vaccination campaign in Finland. PLOS ONE 2013;8(8):e68402.
[295] Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk. PLOS ONE 2014;9(12):e114361.
[296] De la Herrán-Arita AK, Kornum BR, Mahlios J, Jiang W, Lin L, Hou T, et al. CD4+ T cell autoimmunity to hypocretin/orexin and cross-reactivity to a 2009 H1N1 influenza A epitope in narcolepsy. Sci Transl Med 2013;5(216):216ra176.
[297] Rath B, Linder T, Cornblath D, Hudson M, Fernandopulle R, Hartmann K, et al. All that palsies is not Bell's – the need to define Bell's palsy as an adverse event following immunization. Vaccine 2007;26(1):1–14.
[298] Beal MF, Hauser SL. Chapter 376. Trigeminal neuralgia, Bell's Palsy, and other cranial nerve disorders. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/.
[299] Couch RB, Nasal vaccination. *Escherichia coli* enterotoxin, and Bell's palsy. N Engl J Med 2004;350(9):860–1.
[300] Mutsch M, Zhou W, Rhodes P, Bopp M, Chen RT, Linder T, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004;350(9):896–903.
[301] Lewis DJ, Huo Z, Barnett S, Kromann I, Giemza R, Galiza E, et al. Transient facial nerve paralysis (Bell's palsy) following intranasal delivery of a genetically detoxified mutant of *Escherichia coli* heat labile toxin. PLoS ONE 2009;4(9):e6999.
[302] Schwab ME, Suda K, Thoenen H. Selective retrograde transsynaptic transfer of a protein, tetanus toxin, subsequent to its retrograde axonal transport. J Cell Biol 1979;82(3):798–810.
[303] Zurbriggen R, Metcalfe IC, Glück R, Viret JF, Moser C. Nonclinical safety evaluation of *Escherichia coli* heat-labile toxin mucosal adjuvant as a component of a nasal influenza vaccine. Expert Rev Vaccines 2003;2(2):295–304.
[304] Chou CH, Liou WP, Hu KI, Loh CH, Chou CC, Chen YH. Bell's palsy associated with influenza vaccination: two case reports. Vaccine 2007;25(15):2839–41.
[305] Lessa R, Castillo M, Azevedo R, Azevedo F, Azevedo H. Neurological complications after H1N1 influenza vaccination: magnetic resonance imaging findings. Arq Neuropsiquiatr 2014;72(7):496–9.
[306] Greene SK, Kulldorff M, Lewis EM, Li R, Yin R, Weintraub ES, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. Am J Epidemiol 2010;171(2):177–88.
[307] Yih WK, Lee GM, Lieu TA, Ball R, Kulldorff M, Rett M, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009–2010. Am J Epidemiol 2012;175(11):1120–8.
[308] Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. Pediatr Clin North Am 2013;60(6):1489–511.
[309] Neunert CE, Buchanan GR, Imbach P, Bolton-Maggs PH, Bennett CM, Neufeld EJ, et al. Participants. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. Blood 2008;112(10):4003–8.
[310] McMillan R. Antiplatelet antibodies in chronic immune thrombocytopenia and their role in platelet destruction and defective platelet production. Hematol Oncol Clin North Am 2009;23(6):1163–75.
[311] Mantadakis E, Farmaki E, Thomaidis S, Tsalkidis A, Chatzimichael A. A case of immune thrombocytopenic purpura after influenza vaccination: consequence or coincidence? J Pediatr Hematol Oncol 2010;32(6):e227–9.
[312] Oski FA, Naiman JL. Effect of live measles vaccine on the platelet count. N Engl J Med 1966;275(7):352–6.
[313] O'Leary ST, Glanz JM, McClure DL, Akhtar A, Daley MF, Nakasato C, et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. Pediatrics 2012;129(2):248–55.
[314] Kelton JG. Vaccination-associated relapse of immune thrombocytopenia. JAMA 1981;245(4):369–70.
[315] Kaneko H, Ohkawara Y, Nomura K, Horiike S, Taniwaki M, et al. Relapse of idiopathic thrombocytopenic purpura caused by influenza A virus infection: a case report. J Infect Chemother 2004;10:364–6.
[316] Brodin-Sartorius A, Guebre-Egziabher F, Fouque D, Cozon G, Villar E, Laville M, et al. Recurrent idiopathic thrombotic thrombocytopenic purpura: a role for vaccination in disease relapse? Am J Kidney Dis 2006;48(3):e31–4.
[317] Grimaldi-Bensouda L, Michel M, Aubrun E, Leighton P, Viallard JF, Adoue D, et al. A case–control study to assess the risk of immune thrombocytopenia associated with vaccines. Blood 2012;120(25):4938–44.
[318] Villa M, Black S, Groth N, Rothman KJ, Apolone G, Weiss NS, et al. Safety of MF59-adjuvanted influenza vaccination in the elderly: results of a comparative study of MF59-adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy. Am J Epidemiol 2013;178(7):1139–45.
[319] Hur K, Cunningham F, Zhang R, Thakkar B, Eskridge M. Safety of the 2010–2011 influenza vaccinations in the Department of Veteran Affairs, Abstracts of the 28th ICPE 2012. Pharmacoepidemiol Drug Saf 2012:361.
[320] Luke CJ, Lakdawala SS, Subbarao K. Chapter 18: influenza vaccine-live. In: Plotkin S, Orenstein W, Offit P, editors. Vaccine. 6th ed. Philadelphia: Saunders; 2012. p. 294–311.
[321] Rudenko LG, Slepushkin AN, Monto AS, Kendal AP, Grigorieva EP, Burtseva EP, et al. Efficacy of live attenuated and inactivated influenza vaccines in schoolchildren and their unvaccinated contacts in Novgorod, Russia. J Infect Dis 1993;168(4):881–7.
[322] Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, et al. 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 2006;25(10):860–9.
[323] Ashkenazi S, Vertruyen A, Arístegui J, Esposito S, McKeith DD, Klemola T, et al. 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 2006;25(10):870–9.
[324] CDC. Advisory Committee on Immunization Practices (ACIP) recommends a preference for using the nasal spray flu vaccine. Media Statement. June 2014;25. Available at: www.cdc.gov/media/releases/2014/s-acip.html0625.
[325] Public Health England. The Green Book – Influenza (Chapter 19 v8.0); 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/370735/Green_Book_Chapter_19_v8_0.pdf.

[326] National Advisory Committee on Immunization (NACI).; 2013. Available at: www.phac-aspc.gc.ca/naci-ccni/flu-grippe-eng.php#v.
[327] Block SL, Yogev R, Hayden FG, Ambrose CS, Zeng W, Walker RE. Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5–49 years of age. Vaccine 2008;26(38):4940–6.
[328] Vesikari T, Karvonen A, Korhonen T, Edelman K, Vainionpää R, Salmi A, et al. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. Pediatr Infect Dis J 2006;25(7):590–5.
[329] Mallory RM, Yi T, Ambrose CS. Shedding of Ann Arbor strain live attenuated influenza vaccine virus in children 6–59 months of age. Vaccine 2011;29(26):4322–7.
[330] Piedra PA, Yan L, Kotloff K, Zangwill K, Bernstein DI, King J, et al. Safety of the trivalent, cold-adapted influenza vaccine in preschool-aged children. Pediatrics 2002;110(4):662–72.
[331] Edwards KM, Dupont WD, Westrich MK, Plummer Jr WD, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis 1994;169(1):68–76.
[332] Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998;338(20):1405–12.
[333] Swierkosz EM, Newman FK, Anderson EL, Nugent SL, Mills GB, Belshe RB. Multidose, live attenuated, cold-recombinant, trivalent influenza vaccine in infants and young children. J Infect Dis 1994;169(5):1121–4.
[334] Ambrose CS, Yi T, Falloon J. An integrated, multi-study analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2–17 years. Influenza Other Respir Viruses 2011;5(6):389–97.
[335] Bracco Neto H, Farhat CK, Tregnaghi MW, Madhi SA, Razmpour A, Palladino G, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. Pediatr Infect Dis J 2009;28(5):365–71.
[336] Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. J Allergy Clin Immunol 2004;114(2):239–47.
[337] Inoue Y, Shimojo N. Epidemiology of virus-induced wheezing/asthma in children. Front Microbiol 2013;4:391.
[338] Melendi GA, Laham FR, Monsalvo AC, Casellas JM, Israele V, Polack NR, et al. Cytokine profiles in the respiratory tract during primary infection with human metapneumovirus, respiratory syncytial virus, or influenza virus in infants. Pediatrics 2007;120(2):e410–5.
[339] Gern JE, Martin MS, Anklam KA, Shen K, Roberg KA, Carlson-Dakes KT, et al. Relationships among specific viral pathogens, virus-induced interleukin-8, and respiratory symptoms in infancy. Pediatr Allergy Immunol 2002;13(6):386–93.
[340] Takeyama A, Hashimoto K, Sato M, Sato T, Tomita Y, Maeda R, et al. Clinical and epidemiologic factors related to subsequent wheezing after virus-induced lower respiratory tract infections in hospitalized pediatric patients younger than 3 years. Eur J Pediatr 2014;173(7):959–66.
[341] Triantafilou K, Triantafilou M. Ion flux in the lung: virus-induced inflammasome activation. Trends Microbiol 2014;22(10):580–8.
[342] Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J 2004;23(2):138–44.
[343] Breiman RF, Brooks WA, Goswami D, Lagos R, Borja-Tabora C, Lanata CF, et al. A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. Vaccine 2009;27(40):5472–9.
[344] Miller EK, Dumitrescu L, Cupp C, Dorris S, Taylor S, Sparks R, et al. Atopy history and the genomics of wheezing after influenza vaccination in children 6–59 months of age. Vaccine 2011;29(18):3431–7.
[345] Toback SL, Ambrose CS, Eaton A, Hansen J, Aukes L, Lewis N, et al. A postlicensure evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 24–59 months of age. Vaccine 2013;31(14):1812–8.
[346] Piedra PA, Gaglani MJ, Riggs M, Herschler G, Fewlass C, Watts M, et al. Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial. Pediatrics 2005;116:e397–407.
[347] Redding G, Walker RE, Hessel C, Virant FS, Ayars GH, Bensch G, et al. Safety and tolerability of cold-adapted influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J 2002;21(1):44–8.
[348] Gaglani MJ, Piedra PA, Herschler GB, Griffith ME, Kozinetz CA, Riggs MW, et al. Direct and total effectiveness of the intranasal, live-attenuated, trivalent cold-adapted influenza virus vaccine against the 2000–2001 influenza A(H1N1) and B epidemic in healthy children. Arch Pediatr Adolesc Med 2004;158(1):65–73.
[349] King Jr JC, Fast PE, Zangwill KM, Weinberg GA, Wolff M, Yan L, et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. Pediatr Infect Dis J 2001;20(12):1124–31.
[350] Levin MJ, Song LY, Fenton T, Nachman S, Patterson J, Walker R, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. Vaccine 2008;26(33):4210–7.
[351] Halasa N, Englund JA, Nachman S, Weinberg GA, Huber VC, Allison K, et al. Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer. Vaccine 2011;29(24):4110–5.
[352] Boikos C, De Serres G, Lands LC, Boucher FD, Tapiéro B, Daigneault P, et al. Safety of live-attenuated influenza vaccination in cystic fibrosis. Pediatrics 2014;134(4):e983–91.
[353] Slepushkin AN, Obrosova-Serova NP, Burtseva EI, Rudenko LG, Govorkova EA, Vartanyan RV, et al. Comparison of live attenuated and inactivated influenza vaccines in schoolchildren in Russia: I. Safety and efficacy in two Moscow schools, 1987/88. Vaccine 1993;11(3):323–8.
[354] Rudenko LG, Lonskaya NI, Klimov AI, Vasilieva RI, Ramirez A. Clinical and epidemiological evaluation of a live, cold-adapted influenza vaccine for 3–14-year-olds. Bull World Health Organ 1996;74(1):77–84.
[355] Kulkarni PS, Raut SK, Dhere RM. A post-marketing surveillance study of a human live-virus pandemic influenza A (H1N1) vaccine (Nasovac) in India. Hum Vaccin Immunother 2013;9(1):122–4.
[356] Ortiz J, Goswami D, Lewis KDC, Sharmeen AT, Ahmed M, Rahman M, et al. Safety of Russian-backbone seasonal trivalent, live-attenuated influenza vaccine in a phase II randomized clinical trial among children in urban Bangladesh. Vaccine 2014 [in revision].
[357] Brooks A, et al. A randomized, double-blind, placebo-controlled trial on the clinical safety and efficacy of a single dose of trivalent seasonal live-attenuated influenza vaccine among children aged 24 through 59 months in Bangladesh. Vaccine 2015 [in revision].
[371] Feldman S, Wright PF, Webster RG. Use of influenza A virus vaccines in seronegative children: live cold-adapted versus inactivated whole-virus. J Infect Dis 1985;152(6):1212–8.
[372] Skowronski DM, Hottes TS, Chong M, De Serres G, Scheifele DW, Ward BJ, et al. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. Pediatrics 2011;128(2):e276–89.
[373] Domachowske JB, Blatter M, Chandrasekaran V, Liu A, Jain VK, Fries L. A randomized, controlled trial in children to assess the immunogenicity and safety of a thimerosal-free trivalent seasonal influenza vaccine. Pediatr Infect Dis J 2012;31(6):605–15.
[374] Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M, et al. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case–control study in Europe. BMJ 2011;343:d3908.
[375] Szakács A, Darin N, Hallböök T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. Neurology 2013;80(14):1315–21.
[376] O'Flanagan D, Barret AS, Foley M, Cotter S, Bonner C, Crowe C, et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009–December 2010. Euro Surveill 2014;19(17):15–25.
[377] Montplaisir J, Petit D, Quinn MJ, Ouakki M, Deceuninck G, Desautels A, et al. Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec. PLOS ONE 2014;9(9):e108489.
[378] Solberg OD, Mack SJ, Lancaster AK, Single RM, Tsai Y, Sanchez-Mazas A, et al. Balancing selection and heterogeneity across the classical human leukocyte antigen loci: a meta-analytic review of 497 population studies. Hum Immunol 2008;69(7):443–64. Supplemental materials available at: http://pypop.org/popdata/2008/maps/DQB1-0602.gif [accessed 04.06.14].
[379] Arguedas A, Soley C, Abdelnour A, Sales V, Lindert K, Della Cioppa G, et al. Assessment of the safety, tolerability and kinetics of the immune response to A/H1N1v vaccine formulations with and without adjuvant in healthy pediatric subjects from 3 through 17 years of age. Hum Vaccin 2011;7(1):58–66.
[380] Atmar RL, Keitel WA. Preventing pandemic influenza: an update on vaccine development. Infect Med 2007;24(7):292–8.
[381] Bart SA, Hohenboken M, Della Cioppa G, Narasimhan V, Dormitzer PR, Kanesa-Thasan N. A cell culture-derived MF59-adjuvanted pandemic A/H7N9 vaccine is immunogenic in adults. Sci Transl Med 2014;6(234):234ra55.
[382] Luo FJ, Yang LQ, Ai X, Bai YH, Wu J, Li SM, et al. Immunogenicity and safety of three 2010–2011 seasonal trivalent influenza vaccines in Chinese toddlers, children and older adults: a double-blind and randomized trial. Hum Vaccin Immunother 2013;9(8):1725–34.
[383] Kanra G, Marchisio P, Feiterna-Sperling C, Gaedicke G, Lazar H, Durrer P, et al. Comparison of immunogenicity and tolerability of a virosome-adjuvanted and a split influenza vaccine in children. Pediatr Infect Dis J 2004;23(4):300–6 [Erratum in: Pediatr Infect Dis J 2004;23(6):503].
[384] Scheifele DW, Ward BJ, Dionne M, Vanderkooi O, Langley JM, Dobson S, et al. Evaluation of adjuvanted pandemic H1N1(2009) influenza vaccine after one and two doses in young children. Pediatr Infect Dis 2011;30(5):402–7.
[385] Solares AR, Aragon CG, Pivaral RU, Prado-Cohrs D, Sales-Carmona V, Pellegrini M, et al. Safety and immunogenicity profiles of an adjuvanted seasonal influenza vaccine in Guatemalan children. J Infect Dev Ctries 2014;8(9):1160–8.
[386] Van Buynder PG, Frosst G, Van Buynder JL, Tremblay FW, Ross A, Jardine C, et al. Increased reactions to pediatric influenza vaccination following concomitant pneumococcal vaccination. Influenza Other Respir Viruses 2012;7(2):184–90.
[387] Messerschmitt PJ, Abdul-Karim W, Iannotti JP, Gobezie RG. Progressive osteolysis and surface chondrolysis of the proximal humerus following influenza vaccination. Orthopedics 2012;35(2):e283–6.
[388] Robinson AP, Harp CT, Noronha A, Miller SD. The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. Handb Clin Neurol 2014;122:173–89.

[389] Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013;19(10):1261–7, http://dx.doi.org/10.1177/1352458513484547.
[390] Fujii K, Suyama M, Chiba K, Okunushi T, Oikawa J, Kohno Y. Acute disseminated encephalomyelitis following 2009 H1N1 influenza vaccine. Pediatr Int 2012;54(4):539–41.
[391] Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. Autoimmun Rev 2014;13(3):215–24.
[392] Waubant E, Mowry EM, Krupp L, Chitnis T, Yeh EA, Kuntz N, et al. Common viruses associated with lower pediatric multiple sclerosis risk. Neurology 2011;76(23):1989–95.
[393] Waubant E, Mowry EM, Krupp L, Chitnis T, Yeh EA, Kuntz N, et al. Antibody response to common viruses and human leukocyte antigen-DRB1 in pediatric multiple sclerosis. Mult Scler 2013;19(7):891–5.
[394] Farez MF, Ysrraelit MC, Fiol M, Correale J. H1N1 vaccination does not increase risk of relapse in multiple sclerosis: a self-controlled case-series study. Mult Scler 2012;18(2):254–6.
[395] Medical Products Agency (Lakemedelsverket). Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations: results of a case inventory study by the MPA in Sweden during 2009–2010; 2011. Available at https://lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandermrix_110630.pdf.
[396] Dauvilliers Y, Arnulf I, Lecendreux M, Monaca Charley C, Franco P, Drouot X, et al., Narcoflu-VF Study Group. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain 2013;136(Pt 8):2486–96.
[397] Dourmashkin RR. What caused the 1918–30 epidemic of encephalitis lethargica? J R Soc Med 1997;90(9):515–20.
[399] Sendi P, Locher R, Bucheli B, Battegay M. Intranasal influenza vaccine in a working population. Clin Infect Dis 2004;38(7):974–80.
[400] Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT, VAERS Working Group. A potential signal of Bell's palsy after parenteral inactivated influenza vaccines: reports to the Vaccine Adverse Event Reporting System (VAERS) – United States, 1991–2001. Pharmacoepidemiol Drug Saf 2004;13(8):505–10.
[401] Stowe J, Andrews N, Wise L, Miller E. Bell's palsy and parenteral inactivated influenza vaccine. Hum Vaccin 2006;2(3):110–2.
[402] Lee ST, Choe YJ, Moon WJ, Choi JW, Lee R. An adverse event following 2009 H1N1 influenza vaccination: a case of acute disseminated encephalomyelitis. Korean J Pediatr 2011;54(10):422–4.
[403] Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. Br J Clin Pharmacol 2003;55(1):107–11.
[404] Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch Dis Child 2001;84(3):227–9.
[405] Rajantie J, Zeller B, Treutiger I, Rosthöj S, NOPHO ITP Working Group and Five National Study Groups. Vaccination associated thrombocytopenic purpura in children. Vaccine 2007;25(10):1838–40.
[406] Liu C, Polakowski L, Divan HA, Lu Y, Izurieta H, Selvam N. Idiopathic thrombocytopenic purpura after seasonal influenza vaccination. Pharmacoepidemiol Drug Saf 2014;23(S1):1–497.
[407] Steinhoff MC, Halsey NA, Fries LF, Wilson MH, King J, Burns BA, et al. The A/Mallard/6750/78 avian-human, but not the A/Ann Arbor/6/60 cold-adapted, influenza A/Kawasaki/86 (H1N1) reassortant virus vaccine retains partial virulence for infants and children. J Infect Dis 1991;163(5):1023–8.
[408] Cano M. Interim influenza vaccine safety update: live attenuated influenza vaccine and inactivated influenza vaccine in persons <18 years of age, US, 2013–14. In: Presentation at ACIP Influenza Working Group Meeting. 2014.
[409] Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med 2015;7(July (294)):294ra105, http://dx.doi.org/10.1126/scitranslmed.aab2354.