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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