

# Safety of Trivalent Inactivated Influenza Vaccine in Children 6 to 23 Months Old

Simon J. Hambidge, MD, PhD

Jason M. Glanz, PhD

Eric K. France, MD, MSPH

David McClure, PhD

Stanley Xu, PhD

Kristi Yamasaki, PharmD

Lisa Jackson, MD, MPH

John P. Mullooly, PhD

Kenneth M. Zangwill, MD

S. Michael Marcy, MD

Steven B. Black, MD

Edwin M. Lewis, MPH

Henry R. Shinefield, MD

Edward Belongia, MD

James Nordin, MD

Robert T. Chen, MD, MA

David K. Shay, MD, MPH

Robert L. Davis, MD, MPH

Frank DeStefano, MD, MPH

for the Vaccine Safety Datalink Team

INFLUENZA IS A LEADING VACCINE-preventable cause of morbidity and mortality in the United States. Children younger than 2 years experience higher morbidity from influenza than any other age group except individuals older than 65 years.<sup>1-4</sup> Although the case-fatality rate in young children with influenza is not as high as in the elderly, hospitalization rates from severe illness are as high as 3 per 1000 children 6 to 23 months old and as high as 9 per 1000 children younger than 6 months.<sup>5</sup> Furthermore, among young children with influenza, outpatient visits to a clinic

**Context** Beginning with the winter season of 2004-2005, influenza vaccination has been recommended for all children 6 to 23 months old in the United States. However, its safety in young children has not been adequately studied in large populations.

**Objective** To screen for medically attended events in the clinic, emergency department, or hospital after administration of trivalent inactivated influenza vaccine in children 6 to 23 months old.

**Design, Setting, and Participants** Retrospective cohort using self-control analysis, with chart review of significant medically attended events at 8 managed care organizations in the United States that comprise the Vaccine Safety Datalink. Participants were all children in the Vaccine Safety Datalink cohort 6 to 23 months old who received trivalent inactivated influenza vaccine between January 1, 1991, and May 31, 2003 (45 356 children with 69 359 vaccinations).

**Main Outcome Measure** Any medically attended event significantly associated with trivalent inactivated influenza vaccine in risk windows 0 to 3 days, 1 to 14 days (primary analysis), 1 to 42 days, or 15 to 42 days after vaccination, compared with 2 control periods, one before vaccination and the second after the risk window. All individual ICD-9 codes as well as predefined aggregate codes were examined.

**Results** Before chart review, only 1 diagnosis, gastritis/duodenitis, was more likely to occur in the 14 days after trivalent inactivated influenza vaccine (matched odds ratio [OR], 5.50; 95% confidence interval [CI], 1.22-24.81 for control period 1, and matched OR, 4.33; 95% CI, 1.23-15.21 for control period 2). Thirteen medically attended events were less likely to occur after trivalent inactivated influenza vaccine, including acute upper respiratory tract infection, asthma, bronchiolitis, and otitis media. After chart review, gastritis/duodenitis was not significantly associated with trivalent inactivated influenza vaccine (matched OR, 4.00; 95% CI, 0.85-18.84 for control period 1; matched OR, 3.34; 95% CI, 0.92-12.11 for control period 2).

**Conclusions** In the largest population-based study to date of the safety of trivalent inactivated influenza vaccine in young children, there were very few medically attended events, none of which were serious, significantly associated with the vaccine. This study provides additional evidence supporting the safety of universally immunizing all children 6 to 23 months old with influenza vaccine.

JAMA. 2006;296:1990-1997

www.jama.com

**Author Affiliations:** Clinical Research Unit, Kaiser Permanente Colorado (Drs Hambidge, Glanz, France, McClure, Xu, and Yamasaki), Community Health Services, Denver Health, and Department of Pediatrics, University of Colorado School of Medicine (Dr Hambidge), and Department of Preventive Medicine and Biostatistics, University of Colorado School of Medicine (Drs Hambidge, Glanz, and France), Denver; Center for Health Studies, Group Health Cooperative, Seattle, Wash (Dr Jackson); Center for Health Research, Northwest Kaiser Permanente, Portland, Ore (Dr Mullooly); UCLA Center for Vaccine Research, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center,

Calif (Dr Zangwill); Southern California Kaiser Permanente, Panorama City (Dr Marcy); Kaiser Permanente Vaccine Study Center, Northern California Kaiser Permanente, Oakland (Dr Black and Mr Lewis); University of California, San Francisco (Dr Shinefield); Marshfield Clinic Research Foundation, Marshfield, Wis (Dr Belongia); Health Partners Research Foundation, Minneapolis, Minn (Dr Nordin); Centers for Disease Control and Prevention, Atlanta, Ga (Drs Chen, Shay, Davis, and DeStefano). **Corresponding Author:** Simon J. Hambidge, MD, PhD, Clinical Research Unit, Kaiser Permanente Colorado, PO Box 378066, Denver, CO 80237-8066 (simon.hambidge@dhha.org).

or emergency department (ED) are 10 to 250 times as common as hospitalizations.<sup>6</sup>

The trivalent inactivated influenza vaccine has been in use for decades to prevent influenza infection; the vaccine currently in use in the United States has been available since 1981, with annual antigenic modifications to reflect the predominant 3 strains of circulating influenza virus. Until recently, its use in children was recommended only for individuals with known chronic medical conditions that could put them at higher risk from influenza infection, such as asthma. Based on increasing evidence of high morbidity from influenza infection in young children, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommended use of trivalent inactivated influenza vaccine in all children 6 to 23 months old, including healthy children with no chronic medical condition, beginning in the winter season of 2004-2005.<sup>7</sup> By January 31, 2005, 48% of all children in this age group in the United States had received trivalent inactivated influenza vaccine, an unprecedented high.<sup>8</sup>

Influenza vaccine has a good record of safety,<sup>9-15</sup> although there have been documented rare complications from some annual formulations of vaccine.<sup>16-18</sup> A population-based study of the safety of trivalent inactivated influenza vaccine in children 0 to 18 years old (mean age, 10 years) found very few medically plausible associations, none of them serious.<sup>14</sup> However, this study had data on just 8476 vaccinations in children 6 to 23 months old. A recent study on trivalent inactivated influenza vaccine safety in children in this younger age group had data on fewer than 3700 vaccinated children, and thus had little power to detect most potential adverse events.<sup>19</sup> The current report describes a large population-based study of 69 391 vaccinations to evaluate the safety of trivalent inactivated influenza vaccine in very young children.

## METHODS

### Study Design and Setting

We used a retrospective cohort to examine the risk of medically attended events after trivalent inactivated influenza vaccine in children 6 to 23 months old. We assembled a large cohort of children vaccinated against influenza and conducted a case-only analysis, based on the case-crossover method,<sup>20</sup> for each outcome of interest. We used this method to test the following hypothesis: given that a child has received medical care for any reason, the odds are no greater that the resultant diagnosis has occurred in a postvaccination risk window than in a control period temporally unrelated to vaccination. For any outcomes that were positively associated with influenza vaccination in our primary analysis, we performed a self-controlled case series analysis,<sup>21-24</sup> controlling for age and season.

The setting for this study was the Vaccine Safety Datalink project, funded by the Centers for Disease Control and Prevention (CDC), which links large administrative databases from 8 managed care organizations.<sup>25</sup> The institutional review boards at each of the managed care organizations approved this study, and agreed that informed consent from individuals was not required.

Our primary outcome measure was any medically attended event associated with trivalent inactivated influenza vaccine in a 14-day risk window after vaccination when compared with 2 control periods, 1 before and 1 after vaccination. A secondary hypothesis-generating outcome measure was any medically attended event more likely to occur after trivalent inactivated influenza vaccine in any of the risk windows defined in the next section, when compared with only one of the prevaccination or postvaccination control periods.

### Study Population and Analysis

All children 6 to 23 months old who received a trivalent inactivated influenza vaccine from 1991-2003 were eligible for the analyses. From this population of vaccinated children, we

identified any child with a medically attended event in 1 of 3 medical settings (outpatient clinic, ED, or inpatient hospital). Of these children, those with a medically attended event in 1 of 4 predefined risk windows (days postvaccination: 0-2 or 1-3; 1-14; 15-42; and 1-42) were eligible for the analysis. Separate cohort populations were created for each of these risk windows, and within each cohort a nested case-crossover analysis was conducted. Of note, the 3-day risk window in the outpatient setting included days 1 to 3, because inclusion of day 0 (the day of vaccination) has been shown to result in spurious signals when using self-control methods with outpatient data.<sup>14,26</sup> However, for analyses of the risk of medically attended events that occurred in the ED and inpatient settings, we included days 0 to 2 to detect any potentially serious medically attended event that may have occurred on the day of vaccination.

In the 14-day risk window (our primary analysis), any medically attended event (ICD-9-CM code) that occurred at least once in at least 1 child within the 14 days was included in the analysis. The odds of a medically attended event occurring between days 1 to 14 after vaccination were compared with the odds of a medically attended event occurring in 1 of 2 control periods. The first control period was 15 to 28 days prior to vaccination, while the second control period was 15 to 28 days after vaccination. Because physicians tend to administer vaccines to healthy children, medically attended event incidence rates in the 1 to 14 days before vaccination may underestimate true background rates (the "healthy vaccinee" effect).<sup>27</sup> We therefore excluded days 1 to 14 prior to vaccination from the analysis. If a control period and risk window from 2 different trivalent inactivated influenza vaccine injections given to 1 child in the same influenza season overlapped, the control period containing the overlap was excluded from the analysis.

For the 3-day risk window, the first control period was 15 to 17 days prior

to vaccination, while the second control period was 15 to 17 days after vaccination. For the 15- to 42-day risk window, the control periods were days 15 to 42 prior to vaccination and days 43 to 70 after vaccination. For the 1- to 42-day risk window, the control periods were days 15 to 56 prior to vaccination and days 43 to 84 after vaccination.

The case-crossover analysis provides a means to control for potential unmeasured confounding variables that did not vary over time, such as existing chronic health disorders, race or ethnicity, and educational level. Although this method avoids bias caused by comparing dissimilar populations (such as vaccinated and unvaccinated children), it can give biased results with time-varying covariates (for instance, seasonal variation) if the time-varying factors are not explicitly adjusted in the regression analyses.<sup>22,24</sup> Therefore, we conducted a self-control case-series analysis on any outcome that was positively associated with influenza vaccination with respect to both control periods. This analysis was conducted using conditional Poisson regression to calculate incidence rate ratios controlling for age and season.<sup>23</sup>

The case-crossover data were analyzed with conditional logistic regression to generate matched odds ratios (ORs), treating the exposure and control period for each vaccinated case as a matched pair. When using conditional logistic regression, only discordant pairs are analyzed; individuals who experience an event in both the exposure and control periods are dropped from the analysis.<sup>28</sup> All analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC).

All medically attended events that demonstrated an increased risk after vaccination and were significant with respect to both control periods, as well as medically plausible positive associations with matched ORs greater than 2.0 and *P* values of .20 or less with respect to at least 1 of the 2 control periods, underwent medical chart reviews to exclude medically attended events due to causes other than trivalent inactivated

influenza vaccine. These reviews were blinded to whether the event occurred in a risk window or control period. Diagnoses with no biologic plausibility of association with trivalent inactivated influenza vaccine were determined by agreement of all the authors prior to chart review and were excluded (for example, open wound of face, redundant prepuce and phimosis, and refractive error of eyes).

### Medically Attended Events

Medically attended events were defined by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes. Because it is possible that an individual code may not have the power to detect an adverse outcome, we also examined aggregate codes representing groupings of clinically related individual ICD-9 codes. These aggregate codes were determined in advance by the authors and derived in part from grouped codes used in prior work.<sup>14,29</sup> We also examined aggregate codes for complications due to vaccination (including "anaphylactic shock due to serum"), and other potentially serious diagnoses such as respiratory failure, apnea, and hypotension.

For the 3-day, 15- to 42-day, and 1- to 42-day exposure periods, we examined selected prespecified ICD-9 and aggregate codes. For the 3-day risk window, we were interested in acute reactions to the vaccine, such as allergic reaction (including urticaria and serum reaction), cellulitis and skin infections, conjunctivitis, fever, headache, limb soreness and swelling, rash, seizures, and unspecified adverse events after vaccination. In the 15- to 42-day and 1- to 42-day risk windows, we were interested in possible delayed reactions to immunization that might occur via immune-mediated mechanisms. In particular, given the rare association of Guillain-Barré syndrome (GBS) with some annual formulations of trivalent inactivated influenza vaccine in the past,<sup>17</sup> we screened for neurologic diagnoses, including GBS, neuropathies, and demyelinat-

ing disease. Exact ICD-9 codes are available from the authors on request.

For any ICD-9 code that was more likely to occur in a risk window after vaccination compared with both control periods, we also conducted a sub-analysis on healthy children: those without an underlying medical condition that would put them at increased risk from influenza infection.

### RESULTS

A total of 45 356 children aged 6 to 23 months received 69 391 influenza vaccinations in the Vaccine Safety Datalink cohort from 1991-2003. Of these, 16 536 (36%) had a medical condition that put them at higher risk of complications from influenza infection; the rest were healthy children. For the 14-day risk window (*n* = 67 919 vaccinations), we analyzed data from 21 114 outpatient, 1295 ED, and 1264 inpatient medical encounters. This risk window generated more than 2700 regression models, of which 745 had an OR greater than 1.0.

After analysis of ICD-9 codes without chart review, 14 individual conditions were significantly more or less likely to occur within the risk window of 14 days after vaccination compared with both the prevaccination (days 15-28 before vaccination) and the postvaccination (days 15-28 after vaccination) control windows (TABLE 1). For all but 1 condition, this association was negative, ie, there were more visits for that diagnosis in either of the 2 control periods than in the 14-day risk window after trivalent inactivated influenza vaccine. All 14 conditions were seen in the outpatient setting. The condition that had a positive association was gastritis/duodenitis (matched OR, 5.50; 95% confidence interval [CI], 1.22-24.81 for control period 1, and matched OR, 4.33; 95% CI, 1.23-15.21 for control period 2). After chart review to exclude any medically attended events clearly due to other causes than trivalent inactivated influenza vaccine, gastritis/duodenitis was not significantly associated with vaccination: control period 1 matched OR,

4.00; 95% CI, 0.85-18.84; control period 2 matched OR, 3.33; 95% CI, 0.92-12.11. No conditions were significantly more likely to occur within either the 3-day (n=69 391 vaccinations), the 1- to 42-day (n=28 249 vaccinations), or the 15- to 42-day (n=30 624 vaccinations) risk windows compared with both control windows.

In self-control case-series analysis of the only outcome that was more likely to occur after influenza vaccination, we found an increase in gastritis/duodenitis, while adjusting for age of child and time of year: incidence rate ratio, 4.54 (95% CI, 1.90-10.86).

In a subanalysis of those 28 820 children with no underlying medical condition that would put them at increased risk of complications of influenza infection, the increased odds of gastritis/duodenitis was similar to that seen for the full population: matched OR, 4.50 (95% CI, 0.97-20.83) for both control periods.

A total of 56 distinct medically attended events met predefined screening criteria with reference to at least 1 control period; of these, 16 were deemed medically implausible. The remaining 40 medically attended events underwent chart review to determine possible association with trivalent inactivated influenza vaccine. Of 540 charts, 332 (61%) were excluded from the final analysis for the following reasons: the diagnosis was a chronic condition that was not worse at the medical visit (156/332=47% of excluded charts), the medically attended event was a follow-up visit for a condition that was not acute (n=23, 7%), the medically attended event was clearly indicated in the chart as not due to influenza vaccine (n=56, 17%), no chart was available for review (n=47, 14%), the patient did not have the diagnosis (n=3, 1%), or other (for example, medically implausible as in lymphadenitis that was not located near the extremity in which trivalent inactivated influenza vaccine was administered, n=46, 14%).

The majority of medically attended events excluded from the final analy-

**Table 1.** Medically Attended Events Defined by Individual ICD-9 Codes That Were More or Less Likely to Occur After Influenza Vaccination Compared With Both Control Periods Among Children 6 to 23 Months Old, 1991-2003\*

Diagnosis	No. of Medically Attended Events†	Matched Odds Ratio (95% Confidence Interval)‡	
		Control Period 1	Control Period 2
Acute upper respiratory tract infection	2340	0.74 (0.69-0.78)	0.81 (0.77-0.85)
Otitis media	1958	0.77 (0.71-0.82)	0.76 (0.72-0.80)
Asthma	912	0.69 (0.63-0.76)	0.80 (0.73-0.87)
Dyspnea	338	0.67 (0.58-0.78)	0.87 (0.76-1.00)
Cough	202	0.67 (0.55-0.82)	0.84 (0.71-0.99)
Pneumonia	190	0.82 (0.67-1.00)	0.82 (0.68-0.99)
Acute bronchiolitis	179	0.74 (0.60-0.92)	0.79 (0.66-0.94)
Other atopic dermatitis	156	0.76 (0.61-0.96)	0.75 (0.62-0.91)
Dermatitis	141	0.77 (0.60-0.97)	0.70 (0.58-0.86)
Trachea/bronchus disease	33	0.46 (0.30-0.71)	0.56 (0.37-0.85)
Cellulitis	22	0.54 (0.31-0.95)	0.53 (0.32-0.88)
Impacted cerumen	20	0.32 (0.17-0.59)	0.51 (0.32-0.82)
Gastritis/duodenitis‡	12	5.50 (1.22-24.81)	4.33 (1.23-15.21)
Brain injury	8	0.33 (0.15-0.74)	0.35 (0.16-0.78)

\*Outpatient clinics were the settings for all medically attended events.

†Mean number of medically attended events in risk window using both control periods.

‡P<.05 with respect to both control period 1 (15-28 days before vaccination) and control period 2 (15-28 days after vaccination). All associations are for the 14-day risk window; there were no ICD-9 codes significantly associated with trivalent inactivated influenza vaccine in either the 3-day or 42-day risk windows.

sis involved a routine follow-up visit for a child with a chronic condition who was vaccinated with trivalent inactivated influenza vaccine. For instance, all 22 visits for diabetes mellitus were excluded from the final analysis for the following reasons: the visit was to an endocrinologist or diabetes clinic for routine diabetes care, not for a worsening of the diabetes (9 visits); the visit was for an unrelated acute problem such as otitis media with diabetes coded as a secondary diagnosis (6 visits); the visit was actually a phone call with the primary physician's office to discuss glucose control (2 visits); the visit was a routine diabetes check-up with the primary physician (1 visit); the patient did not have diabetes (possible miscoding, 1 visit); and no chart was available for review (3 visits).

Eleven diagnoses were more likely to occur in a risk window after vaccination compared with at least 1 control period with an OR of greater than 2.0 and a P value of less than .20 (TABLE 2). In addition to gastritis/duodenitis (discussed previously), 4 diagnoses (convulsions, lymphadenitis, noninfectious gastroenteritis, and sickle cell

anemia) were statistically more likely to occur in the 14 days after vaccination than in at least 1 control period (in all cases this was control period 1). None of these associations were significant after chart review (Table 2).

### Other Conditions

Because of a recent report to the Vaccine Adverse Events Reporting System (VAERS) of a signal for febrile seizures in the 3 days after trivalent inactivated influenza vaccine administration in young children,<sup>30</sup> we examined the association for convulsions in the 1- to 14-day window in more detail. After chart review, 22 of 24 (92%) of convulsions in the risk window were found to be febrile convulsions. In contrast to the VAERS report, we did not see a signal for convulsions in the 3-day risk window; in fact, there was only 1 febrile seizure in the Vaccine Safety Datalink data set in the 3 days after trivalent inactivated influenza vaccine (on day 3). In the 14-day risk window, 17 of the 24 seizure cases occurred between days 7 and 14 after vaccination, a time when the measles-mumps-rubella (MMR) vaccine is

known to cause an increased risk for febrile seizures.<sup>31</sup> When all of the children who received MMR on the same day as trivalent inactivated influenza vaccine (9 cases and 1 control) were excluded from the analysis, the matched OR for convulsions in the ED in the 14 days after trivalent inactivated influenza vaccine was 1.36 (95% CI, 0.63-2.97). Of note, 9 of 24 seizures (38%) that occurred in the 14-day risk window, and 4 of 12 (33%) in the control

period, were in children who had experienced a prior seizure.

Two sets of medically attended events had borderline significant associations with trivalent inactivated influenza vaccine in the 1- to 42-day risk window, both with respect to control period 1: convulsions in the ED (matched OR, 1.93; 95% CI, 1.01-3.68) and the aggregate code for epilepsy in the ED (matched OR, 2.00; 95% CI, 1.05-3.80). For the aggregate epi-

lepsy code (ICD-9 code 780.3), 27 of the 28 exposed cases were convulsions, which was due to the signal for convulsions in the overlapping 1- to 14-day risk window. We did not see a separate signal for the convulsions code in the 15- to 42-day risk window.

We also examined 2 diagnoses that have been previously linked with trivalent inactivated influenza vaccine.<sup>17,18,32</sup> An increased risk for GBS was noted after swine influenza vaccine in 1976-1977; GBS continues to be reported to VAERS in the 6 weeks after influenza vaccination in adults, on the order of 1 report for every million doses administered.<sup>17</sup> In our cohort of children 6 to 23 months old, there were only 2 children with a diagnosis of GBS and neither child was coded for the syndrome during any of our 4 risk windows. The second diagnosis of note is the oculorespiratory syndrome, including red eyes, respiratory symptoms, and facial swelling, which has been reported after administration of trivalent inactivated influenza vaccine.<sup>18,32</sup> We found no increased signal in any cohort or medical setting for conjunctivitis, either as an individual ICD-9 code or as part of the aggregate code for eye symptoms.

## COMMENT

This large population-based screening study was designed to detect an increase in health care utilization after administration of trivalent inactivated influenza vaccine to children 6 to 23 months old, for whom influenza vaccine is now universally recommended. Given the large number of outcomes assessed, we found very few associations, thereby providing overall reassurance supporting the safety of the vaccine in this age group.

The only positive association with increased risk with respect to both control periods was gastritis/duodenitis in the 14-day risk window in the outpatient clinic setting. In addition, noninfectious gastroenteritis in the ED was increased with respect to 1 control period. On chart review, almost all cases were acute episodes of vomiting, diarrhea, or

**Table 2.** Medically Attended Events That Met Screening Criteria in 3- and 14- Day Risk Windows After Influenza Vaccination Among Children 6 to 23 Months Old, 1991-2003\*

Medically Attended Event and Setting	Days	Control Period	No. of Cases, Risk Window/Control Period†	Matched OR (95% CI)	
				Automated	Chart Review‡
Anemia					
Inpatient	14	1	10/3	3.33 (0.92-12.11)	
Inpatient	14	2	10/8	1.25 (0.49-3.17)	
Convulsions					
ED	14	1	33/15	2.20 (1.19-4.05)	2.00 (1.00-4.00)
ED	14	2	36/27	1.33 (0.81-2.20)	
Gastritis/duodenitis					
Outpatient	14	1	11/2	5.50 (1.22-24.81)	4.00 (0.85-18.84)
Outpatient	14	2	13/3	4.33 (1.23-15.21)	3.33 (0.92-12.11)
General symptoms					
ED	14	1	6/2	3.00 (0.61-14.86)	
ED	14	2	6/4	1.50 (0.42-5.32)	
Lymphadenitis					
Outpatient	14	1	13/3	4.33 (1.23-15.21)	4.00 (0.45-35.79)
Outpatient	14	2	12/12	1.00 (0.45-2.26)	
Noninfectious gastroenteritis					
ED	14	1	36/18	2.00 (1.14-3.52)	1.93 (1.01-3.68)
ED	14	2	45/54	0.83 (0.56-1.24)	
Inpatient	14	1	19/9	2.11 (0.95-4.67)	
Inpatient	14	2	19/23	0.82 (0.45-1.52)	
Serum reaction					
Outpatient	14	1	5/2	2.50 (0.49-12.89)	
Outpatient	14	2	7/2	3.50 (0.73-16.85)	
Sickle cell anemia					
Inpatient	14	1	9/1	9.00 (1.14-71.04)	7.00 (0.86-56.90)
Inpatient	14	2	9/6	1.50 (0.53-4.21)	
Urticaria					
Outpatient	3	1	9/4	2.25 (0.69-7.30)	
Outpatient	3	2	9/35	0.26 (0.12-0.53)	
Viral enteritis					
ED	14	1	4/7	0.57 (0.17-1.95)	
ED	14	2	6/2	3.00 (0.61-14.86)	

Abbreviation: ED, emergency department.

\*Screening criteria: all medically attended events with a matched odds ratio greater than 2.0 and *P* value less than .20 that were more likely to occur in a risk window after trivalent inactivated influenza vaccine compared with at least 1 control period (control period 1 = before vaccination, control period 2 = after vaccination). Only diagnoses for which odds ratios could be generated after chart review are shown.

†Number of cases occurring in a risk window after vaccination compared with the number of cases occurring in a control period. The number of cases in a risk window may differ for a given medically attended event for control period 1 vs control period 2, because concordant pairs are dropped from the analysis when using conditional logistic regression.

‡Results after chart review shown for any association with a 95% confidence interval that does not include 1.0 in the automated analysis.

both in previously healthy children. This finding was unexpected. Given the large number of outcomes analyzed, it is certainly possible that this finding is due to chance alone. However, we cannot rule out that it could be a reaction to the vaccine. Alternatively, it is also possible that young children are exposed at a low level to gastrointestinal viruses from other children in the waiting rooms of their physicians' offices when they are getting vaccinated. This association warrants reexamination as trivalent inactivated influenza vaccine coverage in children 6 to 23 months old increases. Fortunately, this diagnosis, even if due to trivalent inactivated influenza vaccine, is generally mild and self-limited.

It is notable that, of the 14 ICD-9 codes that were significant with respect to both control periods, all but one occurred less frequently after vaccination, a pattern that would not be expected from chance alone. Historically, such a finding has frequently been attributed to an artifact of the healthy vaccinee effect, whereby children may be more likely to be vaccinated only when considered healthy by parents and physicians.<sup>27</sup> In our study, 8 of the 13 codes that occurred less frequently after vaccination are diagnoses that are related to conditions of the respiratory tract or ear, nose, and throat. A lower incidence of respiratory diagnoses has been found after administration of a number of vaccines, including MMR,<sup>33</sup> cold-adapted live attenuated influenza vaccine,<sup>34,35</sup> and trivalent inactivated influenza vaccine.<sup>14</sup> While the first 2 vaccines are live viruses and may induce a nonspecific protection against respiratory viruses via an interferon<sup>33,35</sup> or other cytokine response, it is less clear that an inactivated virus vaccine would induce such an effect.

There is a modest amount of literature regarding hypothesized nonspecific effects of vaccination from observational studies, mostly from developing countries, that can only be resolved by randomized trials.<sup>36</sup> While the Vaccine Safety Datalink does not face many of the data limitations of these other studies, it is still an observational study.

Therefore further investigation is required to determine if the lower occurrence of medical visits for diseases of the respiratory tract and ear, nose, and throat seen after trivalent inactivated influenza vaccine in children is due to confounding from a healthy vaccinee effect or due to a protective effect of the vaccine itself.

As might be expected with a screening study of large administrative databases, we found several other significant associations. Similar to other studies that used self-control methodology,<sup>14,37</sup> we found a lower incidence of asthma diagnoses after trivalent inactivated influenza vaccine, and the effect sizes were of the same magnitude (ORs, 0.69-0.80; all *P* values < .001). While a lower risk of asthma in the 14 days after trivalent inactivated influenza vaccine is unlikely to represent protection from infection with influenza virus, it may represent a reduction of asthma exacerbations triggered by the upper respiratory infections discussed previously. Alternatively, this finding could be due to the healthy vaccinee effect, or possibly reflect a change in asthma therapy during the vaccination visit that resulted in a decreased risk of asthma exacerbation immediately after the visit.

This study found a lower risk of atopic dermatitis and dermatitis after influenza vaccination in young children. In contrast, our earlier work in older children<sup>14</sup> identified a 2-fold increased risk of atopic dermatitis after trivalent inactivated influenza vaccine, but only with respect to 1 control period. Taken together, these findings suggest either real age-specific differences or a chance association of trivalent inactivated influenza vaccine and this skin condition.

We detected an association with convulsions, almost all of which were febrile convulsions, in the 2 weeks after trivalent inactivated influenza vaccine in comparison with 1 control period. However, febrile convulsions after trivalent inactivated influenza vaccine peaked in the second week after vaccination, a time period not considered compatible with known febrile reac-

tions after a formalin-inactivated vaccine. MMR is known to result in a 3-fold increased risk in the second week after vaccine administration.<sup>31</sup> After exclusion of any child who had received MMR on the same day as trivalent inactivated influenza vaccine, there was no association of trivalent inactivated influenza vaccine with febrile seizures. Thus, it appears we were detecting the known association of MMR and febrile seizures. It is also important to note that despite the large potential for type 1 error in our study, we did not detect any signal for seizures, febrile or otherwise, in the 3-day risk window after trivalent inactivated influenza vaccine. Thus, we did not confirm the signal found in VAERS for febrile seizures in the 2 days after trivalent inactivated influenza vaccine.<sup>30</sup>

In addition to gastritis and convulsions, 2 other diagnoses were more likely to occur in the 14 days after trivalent inactivated influenza vaccine when compared with 1 control period. The first of these was lymphadenitis; on chart review most cases were found to be at sites biologically unrelated to the site of vaccination (for example lymphadenitis of the left posterior neck after trivalent inactivated influenza vaccine was administered in the right thigh). The second of these diagnoses was sickle cell anemia in the inpatient setting. After chart review, 2 cases were excluded (1 was hospitalized for a routine transfusion and was not sick, the other had no medical chart to review). This resulted in 7 children hospitalized with either fever or pain in the 14 days after trivalent inactivated influenza vaccine, compared with 1 in the control period. Although not statistically significant, the serious nature of fever and pain crises in these children suggests the need for a hypothesis-testing study of the safety of trivalent inactivated influenza vaccine in children with sickle cell disease.

One limitation of our large screening study is the potential for type 1 error—rejecting the null hypothesis when it is actually true—due to the large number of associations tested. In a prior vac-

cine safety screening study that used similar self-controlled methodology, the authors addressed this issue by randomly splitting the cohort of vaccinated children into 2 samples.<sup>14</sup> The final analysis was then performed only on positive associations that were significant in both samples. Because our study was limited to children 6 to 23 months old, the study population was approximately one quarter the size of the previous study, which included children 18 years old and younger. Therefore we attempted to minimize type 1 error by using as our primary analysis only those associations that were significant with respect to 1 control period before vaccination and 1 after.

Another limitation is that we only analyzed possible adverse events that resulted in a medical visit. It has been shown that assessing telephone encounters to medical offices greatly increases the reported quantity of events after influenza vaccination.<sup>38</sup> However, our effort was to analyze only those events after vaccination that were serious enough to result in a medical visit. An additional limitation is that despite the large size of this study, confidence limits for many individual medically attended events are still wide, suggesting our study was not powered to detect very rare events.

It should be emphasized that our findings apply only to subvirion or purified surface-antigen influenza vaccines (the "split-virus" vaccines), which are the only products recommended in the United States for children 6 to 23 months old. Serious adverse reactions, including febrile seizures, have been noted after administering influenza B whole virus inactivated vaccine in children younger than 3 years.<sup>39</sup> It is also important to note that there is scant data on the efficacy and effectiveness of influenza vaccine in young children.<sup>40</sup> Studies are ongoing with the data sets used in this safety study to determine the efficacy of influenza vaccination in the prevention of hospitalizations among infants and young children during influenza season.

In summary, we conducted a population-based study using large linked databases to examine the safety of trivalent inactivated influenza vaccine in young children 6 to 23 months old. We found no increased risk for a medical visit for any serious condition in any risk window after vaccination. While our findings offer reassurance regarding the safety of the vaccine in the youngest children, large safety studies of influenza vaccine in children in the newly recommended age group of children 3 to 5 years old are needed. Our study, the largest safety study of trivalent inactivated influenza vaccine in children aged 6 to 23 months, adds to prior evidence that influenza vaccine is safe in infants and young children.

**Author Contributions:** Dr Hambidge had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Hambidge, Glanz, France, Xu, Marcy, Black, Nordin, Chen, Shay, Davis, DeStefano.

**Acquisition of data:** Hambidge, Glanz, McClure, France, Yamasaki, Mullooly, Zangwill, Black, Lewis, Shinefield, Belongia, Nordin, Chen, Shay, Davis, DeStefano.

**Analysis and interpretation of data:** Hambidge, Glanz, McClure, Xu, Jackson, Mullooly, Zangwill, Marcy, Black, Nordin, Chen, Shay, Davis, DeStefano.

**Drafting of the manuscript:** Hambidge, Glanz, France, Yamasaki.

**Critical revision of the manuscript for important intellectual content:** Hambidge, Glanz, McClure, France, Xu, Jackson, Mullooly, Zangwill, Marcy, Black, Lewis, Shinefield, Belongia, Nordin, Chen, Shay, Davis, DeStefano.

**Statistical analysis:** Hambidge, Glanz, McClure, Xu, Mullooly, Zangwill.

**Obtained funding:** France, Chen, Shay, DeStefano.

**Administrative, technical, or material support:** McClure, France, Yamasaki, Jackson, Marcy, Lewis, Nordin, Chen, Shay, Davis, DeStefano.

**Study supervision:** Hambidge, Glanz, France, Yamasaki, Shinefield, Chen, Shay, Davis.

**Financial Disclosures:** Dr France reports having received vaccine study funding from Sanofi Pasteur and MedImmune. Dr Yamasaki reports being a coinvestigator in clinical trials for MedImmune (FluMist) and Adventis (Tdap). Dr Jackson reports having received grant support from GlaxoSmithKline, having received grant support from and working as a consultant for Sanofi Pasteur and Chiron (now Novartis), and serving on the speakers' bureau for Sanofi Pasteur. Drs Mullooly and Nordin report having received grant support from Sanofi Pasteur. Dr Marcy reports working as a consultant for Sanofi Pasteur, Merck, GlaxoSmithKline, MedImmune, and Abbott and serving on the speakers' bureau for Sanofi Pasteur and GlaxoSmithKline. Dr Black and Mr Lewis report having received grant support from Sanofi Pasteur, Chiron, and MedImmune. Dr Shinefield reports having received grant support from and serving on the speakers' bureau for Sanofi Pasteur. The authors report that there was no industry involvement in any aspect of this study. The other authors report no financial disclosures.

**Funding/Support:** Financial support for this study was provided in full by the Centers for Disease Control and Prevention (200-2002-00732), through America's Health Insurance Plans. The manuscript was reviewed and approved through the clearance process of the Centers for Disease Control and Prevention prior to submission. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

**Acknowledgment:** We thank Tracy Lieu, MD, MPH, and Richard Platt, MD, MSc, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care, and Harvard Medical School, Boston, Mass for their contributions to this study, including input on study design and supervisory work. They received no specific compensation for this project.

We acknowledge the excellent work of the following members of the Vaccine Safety Datalink team, who provided data management, programming, or project management to assemble the Vaccine Safety Datalink files: Marcia Cunningham, MA, and Ronald Norman (Kaiser Permanente Colorado), James Baggs, PhD (Centers for Disease Control and Prevention, Atlanta, Ga), Katherine H. Hohman, MPH, and Xian-Jie Yu, MPH (Harvard Pilgrim Health Care, Boston, Mass), JoAnn Habakangas, Troy Scott, Darren Malais, Anil Vora, and Patti Benson, MPH (Group Health Cooperative, Seattle, Wash), Amy Butani, Kristi Paulsen, Kelly Fillbrandt, and Leslie Kuckler, MPH (Health Partners Research Foundation, Minneapolis, Minn), Eileen Eriksen, MPH, Zendi Solano, Jeff-Oliver Delacruz, Jerri McIlhagga, and Cathy Martinez (UCLA Center for Vaccine Research, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Calif, and Southern California Kaiser Permanente), Allison Naleway, PhD, Nicholas Berger, Jeremy McCauley, and Kate Konitzer (Marshfield Clinic Research Foundation, Marshfield, Wis), Paula Ray, MPH, Bruce Fireman, MA, Ajit Gemunu de Silva, Diane Carpenter, Joan Schwalbe (Kaiser Permanente of Northern California), and Lois Drew, Karen Riedlinger, MPH, and Jill Mesa (Northwest Kaiser Permanente, Portland, Ore). No compensation was received by individual Vaccine Safety Datalink sites for this study, other than standard Vaccine Safety Datalink funding.

We also acknowledge the support of the staff at America's Health Insurance Plans.

**Previous Presentations:** Preliminary results of this work were presented at a platform session at the Pediatric Academic Societies' annual meeting in San Francisco, Calif on April 30, 2006.

## REFERENCES

- Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med*. 2000;342:232-239.
- Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med*. 2000;342:225-231.
- Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978-1981. *Am Rev Respir Dis*. 1987;136:550-555.
- Rennels MB, Meissner HC; Committee on Infectious Diseases, American Academy of Pediatrics. Technical report: reduction of the influenza burden in children. *Pediatrics*. 2002;110:6 <http://www.pediatrics.org/cgi/content/full/110/6/e80>. Accessed October 1, 2006.
- Grijalva CG, Craig AS, Dupont WD, et al. Estimating influenza hospitalizations among children. *Emerg Infect Dis*. 2006;12:103-109.

6. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. *N Engl J Med*. 2006;355:31-40.
7. Harper SA, Fukuda K, Uyeki TM; Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2004;53(RR-6):1-40.
8. Centers for Disease Control and Prevention. Estimated influenza vaccination coverage among adults and children—United States, September 1, 2004–January 31, 2005. *MMWR Recomm Rep*. 2005;54:304-307.
9. 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;69:404-408.
10. American Lung Association Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med*. 2001;345:1529-1536.
11. Groothuis JR, Levin MJ, Rabalais GP, Meiklejohn G, Lauer BA. Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. *Pediatrics*. 1991;87:823-828.
12. Piedra PA, Glezen WP, Mbawuike I, et al. Studies on reactogenicity and immunogenicity of attenuated bivalent cold recombinant influenza type A (CRA) and inactivated trivalent influenza virus (TI) vaccines in infants and young children. *Vaccine*. 1993;11:718-724.
13. Zangwill KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination. *Pediatr Infect Dis J*. 2004;23:189-200.
14. France EK, Glanz JM, Xu S, et al. Safety of the trivalent inactivated influenza vaccine among children: a population-based study. *Arch Pediatr Adolesc Med*. 2004;158:1031-1036.
15. Skowronski DM, Jacobsen K, Daigneault J, et al. Solicited adverse events after influenza immunization among infants, toddlers, and their household contacts. *Pediatrics*. 2006;117:1963-1971.
16. Ropper AH, Victor M. Influenza vaccine and the Guillain-Barré Syndrome. *N Engl J Med*. 1998;339:1845-1846.
17. Haber P, DeStefano F, Angulo FJ, et al. Guillain-Barré Syndrome following influenza vaccination. *JAMA*. 2004;292:2478-2481.
18. Scheifele DW, Duval B, Russell ML, et al. Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. *Clin Infect Dis*. 2003;36:850-857.
19. Goodman MJ, Nordin JD, Harper P, DeFor T, Zhou XZ. The safety of trivalent influenza vaccine among healthy children 6 to 24 months of age. *Pediatrics*. 2006;117:e821-e826.
20. Maclure M. The case-crossover design: a method for studying transient effects on risk of acute events. *Am J Epidemiol*. 1991;133:144-153.
21. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics*. 1995;51:228-235.
22. Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine*. 2004;22:2064-2070.
23. Whitaker HJ, Farrington CP, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25:1768-1797.
24. Glanz JM, McClure DL, Xu S, et al. Four different study designs to evaluate vaccine safety were equally valid with contrasting limitations. *J Clin Epidemiol*. 2006;59:808-818.
25. Chen RT, Glasser JW, Rhodes PH, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States: the Vaccine Safety Datalink Team. *Pediatrics*. 1997;99:765-773.
26. Tata LJ, West J, Harrison T, Farrington CP, Smith C, Hubbard R. Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease? *Thorax*. 2003;58:835-839.
27. Virtanen M, Peltola H, Paunio M, Heinonen OP. Day-to-day reactogenicity and the healthy vaccinee effect of measles-mumps-rubella vaccination. *Pediatrics*. 2000;106:e62.
28. Liang KY. Extended Mantel-Haenszel estimating procedure for multivariate logistic regressions. *Biometrics*. 1987;43:289-300.
29. Finkelstein JA, Davis RL, Dowell SF, et al. Reducing antibiotic use in children: a randomized trial in 12 practices. *Pediatrics*. 2001;108:1-7.
30. McMahon AW, Iskander J, Haber P, 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;115:453-460.
31. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med*. 2001;345:656-661.
32. Orr P; Health Canada; National Advisory Committee on Immunization (NACI). Supplementary statement for the 2002-2003 influenza season: update on oculo-respiratory syndrome in association with influenza vaccination. *Can Commun Dis Rep*. 2002;28(ACS-6):1.
33. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine: a double-blind placebo-controlled trial in twins. *Lancet*. 1986;1:939-942.
34. Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J*. 2004;23:138-144.
35. Piedra PA, Gaglani MJ, Riggs 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-e407. [www.pediatrics.org/cgi/doi/10.1542/peds.2004-2258](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-2258). Accessed October 1, 2006.
36. Fine PE. Non-specific "non-effects" of vaccination. *BMJ*. 2004;329:1297-1298.
37. Kramarz P, DeStefano F, Gargiullo PM, et al. Does influenza vaccination prevent asthma exacerbations in children? *J Pediatr*. 2001;138:306-310.
38. Mullooly JP, Crane B, Chun C. Trivalent inactivated influenza vaccine safety in children: assessing the contribution of telephone encounters. *Vaccine*. 2006;24:2256-2263.
39. 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;88:31-35.
40. Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA; Advisory Committee on Immunization Practices. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2006;55(RR-10):1-42.