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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

Ann W. McMahon, MD*; John Iskander, MD‡; Penina Haber, MPH‡; Soju Chang, MD*; E. Jane Woo, MD*; M. Miles Braun, MD*; and Robert Ball, MD*

ABSTRACT. *Background.* In April 2002, the Advisory Committee on Immunization Practices (ACIP) encouraged providers to vaccinate healthy 6- to 23-month-old infants and children with trivalent influenza vaccine (TIV).

Objectives. To describe adverse events (AEs) reported to the Vaccine Adverse Event Reporting System (VAERS) after TIV vaccination among children <2 years of age and to compare reports before the ACIP guideline (January 1990 to June 2002) and after the ACIP guideline (July 2002 to June 2003).

Methods. VAERS is a passive vaccine safety surveillance system begun by the Food and Drug Administration and the Centers for Disease Control and Prevention in 1990. We reviewed reports to VAERS for children <2 years of age who received TIV, alone or in combination with other vaccines. Influenza seasons were defined as the period from July 1 of one year to June 30 of the following year.

Results. Between 1990 and 2003, VAERS received 166 TIV reports for children <2 years of age. There were 62 reports (37%) after administration of TIV alone and 104 reports (63%) after administration of TIV and ≥ 1 other vaccine. Approximately one third of reports ($N = 61$) were in the post-ACIP guideline period. The 4 most frequent AE coding terms were fever ($N = 59$, 35%), unspecified or urticarial rash (42, 25%), seizure (28, 17%), and injection site reaction (28, 17%). The median number of days from vaccination to symptom onset, the percentage of reports that represented serious AEs, and the gender distribution were similar in the pre-ACIP guideline and post-ACIP guideline periods. The percentage of reports describing an underlying medical condition for the subject decreased from 58% before the ACIP guideline to 37% after the ACIP guideline. Nineteen of 28 seizure reports (68%) described fever with the seizure within 2 days after vaccination. Seizure was the most frequent coding term ($N = 10$, 7 with fever) among 23 serious reports. The annual number of TIV-related VAERS reports for children <2 years of age increased in the post-ACIP guideline period, probably at least in part because

of an increase in the number of vaccinees after the ACIP announcement. The safety profiles in the pre-ACIP guideline and post-ACIP guideline periods were similar.

Conclusions. In October 2003, the ACIP recommended that all healthy children 6 to 23 months of age be vaccinated with TIV, starting in the 2004–2005 influenza season. This study provides generally reassuring, although limited, data regarding the safety of TIV among children in this age range. Continued surveillance for seizures and other clinically significant AEs is warranted and will continue. *Pediatrics* 2005;115:453–460; *influenza vaccine, adverse events, infants.*

ABBREVIATIONS. VAERS, Vaccine Adverse Event Reporting System; TIV, trivalent influenza vaccine; ACIP, Advisory Committee on Immunization Practices; PRR, proportional reporting ratio; AE, adverse event; DC, disease category.

Influenza virus infections cause significant morbidity among young children. Neuzil et al¹ documented annual rates of 95 health care visits, 3.5 hospitalizations, 46 episodes of acute otitis media, and 8 episodes of lower respiratory infection per 1000 healthy children as a result of culture-confirmed influenza virus infection. The rate of each of these events was significantly higher among children <2 years of age, compared with 2- to 5-year-old children.¹ In addition to the considerable morbidity and health care expenditures caused by influenza virus infection among young children, young children may spread influenza virus within the household.²

The efficacy of trivalent influenza vaccine (TIV) among children has been estimated to be between 31% and 91%.^{2,3} The wide range of efficacy estimates is likely attributable in part to seasonal variations in circulating strains of viruses and the composition of the vaccines studied. There have been more safety studies of TIV among adults^{4–7} than among children. Studies among children performed to date suggest that the vaccine is well tolerated,^{3,8,9} although there are limited data on rare potential adverse effects.

TIV has been recommended since 1983 for children ≥ 6 months of age who are at high risk of morbidity and death from influenza virus infection.¹⁰ In April 2002, the Advisory Committee on Immunization Practices (ACIP) encouraged (but did not recommend) providers to vaccinate healthy children 6 to 23 months of age.¹¹ The American Academy of Pediatrics and the American Academy of Family Physicians adopted a similar policy.¹² In October 2003, the

From the *Division of Epidemiology, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland; and †Immunization Safety Branch, Epidemiology and Surveillance Division, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia.

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Address correspondence to Ann W. McMahon, MD, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852. E-mail: mcmahon@cber.fda.gov

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ACIP recommended universal vaccination of infants and children 6 to 23 months of age beginning in the 2004-2005 influenza season.¹² In part as preparation for vaccination of more children of this age, this review compares the adverse event (AE) experience before the guidelines encouraging vaccination of healthy infants with that after the guidelines, as a way of determining whether new AEs would be detected in the new era. A possible reason why different AEs might be detected after implementation of the new guidelines is that, with the larger number of vaccinees 6 to 23 months of age, compared with that before the guidelines, rare vaccine AEs might become evident.¹³

The Vaccine Adverse Event Reporting System (VAERS) is the largest national database of reported AEs after vaccination. Approximately 170 000 reports of AEs have been received through passive reporting from the inception of VAERS in 1990 through May 2004. Because of the national scope of the system, analysis of the VAERS database allows study of AEs that are infrequent.

METHODS

Description of VAERS

VAERS is a passive surveillance system that was established in 1990 and is operated collaboratively by the Centers for Disease Control and Prevention and the Food and Drug Administration. Reports of AEs are submitted to VAERS by vaccine providers, vaccinees, parents, and others. A "serious event" reported to VAERS is defined in the Code of Federal Regulations¹⁴ as a report that, according to the reporter, resulted in life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or death, or an intervention to prevent one of these outcomes. Although manufacturers are required to report to VAERS serious and/or unexpected events and providers have some obligations to report under the National Childhood Vaccine Injury Act of 1986,¹⁵ the vast majority of reporting is voluntary. Reports are coded with Coding Symbols for Thesaurus of Adverse Reaction Terms (referred to hereafter as coding terms).^{16,17} VAERS usually cannot be used to determine causal associations between vaccinees and reported AEs, for the following reasons. (1) A passive surveillance system cannot be used for incidence calculations, because of underreporting, lack of denominator data, and lack of confirmation of the AEs. (2) There is no control group for comparison of AE rates. (3) Case definitions are difficult to apply in VAERS, because of the relative paucity of clinical information in the reports.¹⁸ VAERS has been used effectively to generate hypotheses to be tested in other settings, such as the Vaccine Safety Datalink¹⁹ and various epidemiologic studies.²⁰ In recent years, VAERS data have led to significant public health actions, such as rotavirus vaccine withdrawal²¹ and ACIP adoption of new contraindications for smallpox vaccine for individuals with cardiac risk factors.²²

Report Review

One of 2 physicians (A.W.M. or S.C.) reviewed all VAERS reports for children <2 years of age who were vaccinated between January 1, 1990, and June 30, 2003. We assigned disease categories (DCs) after review for the AEs and compared the DCs with the original coding terms. Relatively minor differences were found between the DCs and the coding terms. Complex cases were reviewed by both physicians and adjudicated with consensus clinical judgment. The DCs were used in preference to coding terms for the majority of the analyses because of the greater accuracy and completeness of data based on physicians' review of the VAERS reports. In determination of the presence or absence of an underlying medical condition, the terminology of the reporter was used, with some interpretation on the part of the reviewers. In particular, if the diagnosis of asthma was given by the reporter or

if prior wheezing was noted, then the underlying medical condition was classified as asthma.

Analysis

Influenza seasons were defined as extending from July 1 of the first year to June 30 of the following year. The date of vaccination, not the VAERS report date, was used to classify reports, because the analysis considered AE reports to be associated with a vaccine with a particular season's formulation. We compared the reports for children <2 years of age who were vaccinated with TIV before the ACIP encouraged vaccination of healthy children of this age (January 1, 1990, to June 30, 2002; pre-ACIP guideline) with those for children who were vaccinated afterward (July 1, 2002, to June 30, 2003; post-ACIP guideline). Data from multiple years before 2002-2003 were aggregated because the number of reports per year was too small for meaningful season-specific analyses. Despite the annual vaccine strain adjustments, there is antigenic similarity in vaccine composition from year to year, and we did not expect differences in reactogenicity from one year to the next. We searched for patterns in AEs according to coding terms, DCs, vaccination date, gender, time to onset, and administration of a single vaccine versus multiple vaccines. Special attention was paid to reports of serious events and deaths. We also conducted a preliminary review (not reported here) of reports from the 2003-2004 influenza season, to look for major changes in patterns, but we did not conduct supplemental case review of all reports because data were not complete at the time of the main analysis. Business Objects software (Business Objects Americas, San Jose, CA) was used for importing of data, and JMP (SAS Institute, Cary, NC) and Stata (Stata Corp, College Station, TX) statistical software packages were used for data analyses.

We estimated the number of 6- to <24-month-old children who received TIV in 2002-2003 by using US Census data for the year 2000.²³ We calculated proportional reporting ratios (PRRs)²⁴⁻²⁶ for all coding terms for TIV vaccinations from January 1, 1990, to June 30, 2003, for children <2 years of age. The PRR is a mathematical tool used to compare the proportion of reported events for TIV with that for other vaccines. We used the PRR to screen for symptoms or conditions meriting additional clinical review. PRR was calculated as follows: $PRR = \frac{[\text{number of reports assigned a given coding term for TIV}]/[\text{total number of reports for TIV}]}{[\text{number of reports assigned a given coding term for comparison vaccines}]/[\text{total number of reports for comparison vaccines}]}$.

The comparison group included all VAERS reports for vaccinees other than TIV for children <2 years of age. We selected for additional review coding terms with PRRs of ≥ 2 involving >3 events, with a χ^2 statistic of ≥ 4 , that were not otherwise selected for review.²⁴

We did not use statistical tests of significance or confidence intervals in our analyses of these VAERS data. The numerous acknowledged limitations of VAERS, including underreporting, selective reporting, lack of a control group, inadequate denominator data for calculation of event rates, and diagnostic uncertainty regarding events, result in the likelihood of large biases being present in VAERS data. Although the effect of confounding can often be reduced through statistical adjustment, bias is very difficult to quantify or to control in nonexperimental studies, especially in analyses of VAERS data, and is likely to be a far greater source of uncertainty than the effect of chance.¹⁸

RESULTS

Number of Reports

Between January 1, 1990, and June 30, 2003, there were 166 reports to VAERS after the administration of TIV to children <2 years of age. The median age of report subjects was 13 months (range: 0-23 months), and 71 of 161 subjects (44%) with reported gender were female. Seven subjects were reported to be <6 months of age at the time of vaccination, outside the label recommendations (see below). Approximately one third of all reports occurred after the ACIP guideline ($N = 61$), ie, 7 times the mean annual number for 12 previous years (mean = 8.75) and 3 times the number reported for the 2001-2002 season

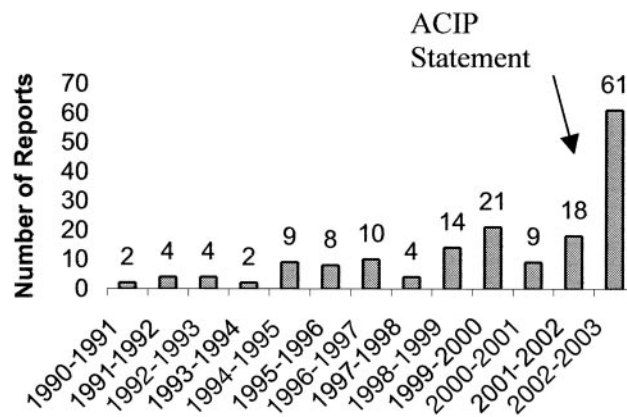


Fig 1. Number of VAERS reports after TIV among children <2 years of age, according to influenza season.

TABLE 1. Characteristics of AE Reports After Administration of TIV Among Children According to Year and Seriousness

	1990–2002 (N = 105)	2002–2003 (N = 61)	1990–2003, Serious Only (N = 23)
TIV only, no. (%)	44 (42)	18 (30)	11 (48)
Onset interval,* d, median (range)	1 (0–470)	1 (0–83)	2 (0–30)
Age, mo, median (range)	13 (0–23)	13 (6–23)	13 (2–23)
Female, no. (%)	44 (44)	27 (45)	11 (50)
Serious, no. (% of reports)	15 (14)	8 (13)	NA
Underlying medical conditions, no. (% of reports)	54 (58)	18 (37)	11 (58)

NA indicates not applicable.

* Interval between vaccination and onset of symptoms.

(N = 18; Fig 1; Table 1). Although there is no adequate estimate of the percentage of children 6 to 23 months of age vaccinated with TIV before 2002, the National Immunization Survey estimated the coverage rate in the 2002–2003 influenza season as $7.4 \pm 0.7\%$.²⁷ On the basis of projections from US Census 2000 data, between 424 667 and 513 403 children 6 to 23 months of age are estimated to have received TIV in 2002–2003 in the United States. Preliminary review of recently available VAERS reports for the 2003–2004 influenza season revealed results similar to those for the 2002–2003 season.

Commonly Reported Events

We reviewed all reports after TIV administration for this age group and assigned ≥ 1 DCs to each report. The 5 most frequently reported DCs were fever (N = 59, 36%), seizure (N = 28, 17%), injection site reaction (N = 28, 17%), unspecified rash (N = 25, 15%), and urticarial rash (N = 17, 10%). The top 14 DCs were the same as the top 14 coding terms, with the exception of diarrhea and lethargy, which were ranked 11th and 12th among the DCs and 21st and 20th among the coding terms, respectively.

Comparison of TIV Alone With TIV and Other Vaccines

We compared the proportions of individual DCs in all reports for children who received TIV alone versus TIV with other vaccines. There were 62 reports (37%) after administration of TIV alone and 104 reports (63%) after administration of TIV and ≥ 1 other vaccines. Six of the 10 DCs that were most

frequent among reports for children who received TIV alone were also most frequent among reports for children who received TIV with ≥ 1 other vaccines (Table 2). The proportion of events with the DCs of unspecified cough, rhinitis, and flu syndrome was 2

TABLE 2. Description of DCs After Physicians' Review of VAERS Reports After Administration of TIV to Children <2 Years of Age, 1990–2003

	No.	%
TIV alone (N = 62)		
Fever	28	45
All seizures	14	23
Unspecified rash	7	11
Cough	6	10
Injection site reaction	5	8
Urticarial rash	6	10
Rhinitis	6	10
Vomiting	4	6
Flu syndrome	3	5
Agitation	2	3
TIV in combination (N = 104)		
Fever	31	30
Injection site reaction	23	22
Injection site reaction not related to TIV*	6	6
Unspecified rash	18	17
All seizures	14	13
Urticarial rash	11	11
Diarrhea	5	5
Vomiting	5	5
Agitation	4	4
Lethargy	4	4

Reports may include >1 DC.

* Injection site reactions that were not at the site where TIV was administered.

to 4 times higher among children who received TIV alone, although the true incidence of these conditions in the 2 populations is unknown. There were 16 total reports coded as flu syndrome, cough, and/or rhinitis on day 0 to 2 after vaccination. A review of these reports indicated that 2 children had a preexisting "cold" or "flu." Eight of these reports specified that the child also had fever.

Comparison of AEs Before and After ACIP Announcement

We compared the AE reports before and after the ACIP guideline. Eight of the 10 most frequent DCs were seen both before and after the ACIP guideline (Table 3), although the incidence of these conditions during these periods is unknown. A smaller proportion ($N = 6$, 10%) of seizure reports was observed after the ACIP guideline, compared with before the ACIP guideline ($N = 22$, 21%). Urticarial rash was present at a 3 times greater proportion in the 2002–2003 influenza season ($N = 11$, 18%), compared with all previous seasons combined ($N = 6$, 6%). The proportions of fever, injection site reactions, unspecified rash, rhinitis, cough, agitation, diarrhea, lethargy, and injection site reactions unrelated to TIV administration for 2002–2003 were similar to those for previous years. The median intervals between vaccination and the onset of symptoms were similar before and after the ACIP guideline (Table 1).

Underlying Medical Conditions

Seventy-two of 142 children (51%) whose medical history was reported had ≥ 1 underlying medical conditions, 58% before the ACIP announcement and 37% after the announcement. The most frequently

TABLE 3. Most Frequent DCs From Physicians' Review of VAERS Reports After Administration of TIV to Children <2 Years of Age

	No.	%
Before ACIP guideline, 1990–2002 ($N = 105$)		
Fever	40	38
All seizures	22	21
Injection site reaction	15	14
Unspecified rash	15	14
Rhinitis	7	7
Cough	6	6
Urticarial rash	6	6
Agitation	4	4
Diarrhea	4	4
Lethargy	4	4
After ACIP guideline, 2002–2003 ($N = 61$)		
Fever	19	31
Injection site reaction	13	21
Injection site reaction not related to TIV*	3	5
Urticarial rash	11	18
Unspecified rash	10	16
All seizures	6	10
Vomiting	5	8
Cough	3	5
Rhinitis	3	5
Agitation	2	3

* Injection site reactions that were not at the site where TIV was administered.

reported underlying medical condition was asthma ($N = 22$, 31% of those with reported underlying conditions) (Table 4). For children with the underlying medical condition of asthma, the most frequently reported AEs included fever ($N = 9$, 41%), seizure ($N = 5$, 23%), injection site reaction ($N = 5$, 23%), urticarial rash ($N = 4$, 18%), and unspecified rash ($N = 3$, 14%).

Serious Reports

Twenty-three serious events (14%) were reported for children <2 years of age after TIV administration. Forty-eight percent of the serious reports were for children who received TIV alone (Table 1). This was slightly greater than the 37% of all reports for children <2 years of age who received TIV alone. A similar proportion (58%) of all serious events with a medical history documented in the VAERS report involved children with underlying medical conditions, compared with the proportion of overall reports (51%). The most frequent DCs for these events were seizure ($N = 10$, 43%, 7 of 10 with fever), fever ($N = 10$, 43%), and rhinitis ($N = 4$, 17%). One case of Guillain-Barré syndrome was reported, involving a 19-month-old male patient with a history ~6 months before vaccination of pneumonia with right middle lobe collapse, pancytopenia, and hepatosplenomegaly. The child developed Guillain-Barré syndrome 10 days after vaccination with TIV. The patient was treated with intravenously administered immunoglobulin and physical therapy, with improvement.

Seizures

Because a large proportion ($N = 10$, 43%) of serious reports were of seizures, we characterized all of the seizure reports more extensively. A total of 28 cases of seizures were reported (17% of all reports), of which 19 (66%) involved fever with seizures within 2 days after vaccination, with no reported alternative explanation for the seizures. One report noted a history of febrile seizures and 1 a seizure disorder. In addition to these 19 reports of seizures with fever, there was 1 other report of seizures with fever, involving a patient who was diagnosed with *Staphylococcus* bacteremia on the day of vaccination. Six of the remaining reports involved patients with nonfebrile seizures within 2 days after vaccination, of

TABLE 4. Number of Reports Describing Children With Underlying Medical Conditions

Underlying Condition	No. of Reports
Asthma	22
Prematurity	10
Congenital heart disease	7
Allergy	7
Seizure disorder	7
Down syndrome	5
Bronchopulmonary dysplasia	5
Eczema	5
Developmental delay	4
Gastroesophageal reflux	3
Other	20
Total reports with ≥ 1 underlying condition	72

Each report could have been assigned >1 condition; the total number of reports with reported medical history was 142.

whom 1 had a seizure disorder and 1 had a twin with a history of febrile seizures. Two additional reports involved patients with new-onset seizures, which occurred 14 and 30 days after vaccination.

Deaths

Three deaths after TIV were reported for children <2 years of age. Two deaths involved children with underlying medical conditions and occurred before the ACIP guideline. The first patient was a 6-month-old male patient with tricuspid atresia and complex congenital heart disease, after multiple cardiac surgical procedures. The patient was found apneic 4.5 hours after vaccination. He was taken to an emergency department and was resuscitated but died after being airlifted to a hospital. The cause of death was thought to be possibly acute cardiac decompensation.

The second death involved a 12-month-old female patient with a history of asthma who experienced weight loss and vomiting 37 days after vaccination and was found to have a greatly elevated plasma glucose concentration of 1310 mg/dL. She was admitted to the hospital and rapidly developed severe cerebral edema, from which she did not recover; she died 45 days after vaccination. The pathologic examination of the body was performed after many of the organs had already been removed. No anatomic diagnosis was made, and the clinical diagnosis was diabetic ketoacidosis and brain death.

The third death occurred after the ACIP guideline. This case involved a 9.5-month-old female patient with no underlying medical condition, who presented 18 days after vaccination with stridor and fever. After 2 doses of racemic epinephrine, the patient experienced cardiopulmonary arrest. She was resuscitated, but the next day she exhibited rapid deterioration, despite intensive care. She was determined to be brain dead and was removed from support. The autopsy showed acute necrotizing laryngotracheitis and acute hemorrhagic bronchopneumonia involving the left and right lower lung lobes. *Haemophilus influenzae* (β -lactamase positive) was recovered from the nasotracheal tube. The cause of death was acute necrotizing laryngotracheitis thought to be caused by *H influenzae*.

Reports for Infants <6 Months of Age

There were 7 reports of AEs among children <6 months of age who received TIV. Two of the children had a history of congenital heart disease, 2 had a history of prematurity, and 1 had a history of asthma. Only 1 of these reports was classified as serious, ie, a report of croup in a 2-month-old patient 17 days after vaccination. Of the nonserious reports, 1 was of seizure 2 days after vaccination for a 2-month-old infant with a history of prematurity, 2 were of cough, 1 was of injection site reaction, 1 was of irritability, and 1 was of fever. The PRR analysis revealed no AEs that were not on the product label or identified already, by other means.

DISCUSSION

Relatively few AEs after TIV among children <2 years of age have been reported to VAERS, and review of the reports revealed that the most frequently reported symptoms and signs were mild; however, seizure, mostly associated with fever, was among the most frequently reported events. Compared with the pre-ACIP guideline period, the average annual number of reports after TIV among children <2 years of age increased sevenfold in the post-ACIP guideline period. This increase is most likely attributable, at least in part, to an increase in the number of vaccine doses administered to children <2 years of age after the 2002 ACIP guideline. However, because of the lack of data on the number of doses of TIV administered to subjects in this age group before the 2002–2003 influenza season, we were not able to estimate the magnitude of the likely increase in vaccination in the latter time period. VAERS has gradually come into wider use, and the total number of annual reports for all vaccines approximately doubled from 1991 to 2003; however, the average number of annual reports for TIV among 6- to 23-month-old children increased sevenfold from 2000 to 2003, which cannot be explained by the general increase alone.

Approximately 40% of children in the reports after the ACIP guideline had an underlying medical condition, representing a decrease from ~60% before the ACIP guideline. The high rate of underlying medical conditions in these reports is undoubtedly attributable, at least in part, to the 1983 recommendation that children with chronic disorders but not healthy children receive TIV. Overall, the characteristics of the pre-ACIP and post-ACIP guideline VAERS-reported events were similar. Although it is impossible to determine from VAERS reports alone, given the lack of denominator and incomplete reporting, it is conceivable that the ACIP guideline stimulated vaccination not only of healthy 6- to 23-month-old children but also of children with underlying medical conditions. In such a case, it would not be surprising that similar safety patterns would be noted among vaccinees before and after the ACIP guideline.

Asthma was noted to be the most frequent underlying medical condition. This classification was given by the reporters or was assigned by the reviewers if asthma or wheezing was mentioned as an underlying condition. Only a subset of children in the 6- to 23-month age group who wheeze actually proceed to develop asthma (as defined in the guidelines for the diagnosis and management of asthma²⁸). It is very difficult to determine which of the children who wheeze in response to respiratory viruses at this age would be most severely compromised if infected with influenza virus. It may be that pediatricians have been offering influenza vaccine to the families of infants who have wheezed in any setting, but data on these details of provider practices are not available.

It is possible that the events described in the TIV VAERS reports for <2-year-old children reflect symptoms of the underlying illnesses of these sub-

jects ("confounding by indication").²⁹ However, the most frequent underlying condition found in these reports was asthma and, with the exception of 1 report of "flu syndrome," the AEs that were reported after TIV administration among asthmatic children <2 years of age were not respiratory in nature. As was true of the TIV reports for this age group as a whole, fever, seizure, and injection site reaction were the most frequent AEs reported for asthmatic subjects. Asthmatic exacerbations were found not to be increased after TIV administration to children in 2 controlled studies.^{19,30}

Sixteen reports of cough, rhinitis, and flu syndrome associated with TIV were submitted. We identified a small group of cases with ≥ 1 of these symptoms occurring within 2 days after vaccination. Because these symptoms are common in this age group, they may be associated with coincidental viral illnesses. Because TIV is inactivated, a biological mechanism for association of these symptoms with TIV would be difficult to support.

Fever was reported after TIV, but it is unclear whether fever is causally associated with TIV administration among children. Fever is common among infants and children <2 years of age and is one of the AEs listed on the product label as being associated with TIV. Placebo-controlled trials of TIV among or including children did not show rates of fever to be significantly increased among vaccines, compared with placebo recipients. In 1977, Wright et al³¹ found no difference in febrile responses of 2326 children 6 months to 18 years of age who received vaccine or placebo. Neuzil et al³ reported similar findings for 791 children 1 to 16 years of age. In an uncontrolled descriptive study, Daubeney et al³² found a 27% rate of fever within 72 hours after TIV administration among 52 high-risk children 6 months to 4 years of age.

Seizures after TIV among <2-year-old subjects made up a large proportion of AE reports, although the absolute number was small. There were 23 serious events, of which 10 were seizures (7 of those being febrile). The fact that seizures were comparatively frequently reported may be attributable, in part, to the perceived seriousness of the event (compared with an AE such as injection site reaction, which may be underreported to a greater degree³³). Febrile seizures, which are alarming but generally benign events, are not uncommon among young children, with a peak incidence at ages 14 to 18 months³⁴ and an annual incidence of 3 cases per 1000 children 6 months to 5 years of age.³⁵ Most controlled trials of TIV administration among children did not report seizures of any kind among study participants,^{3,31} although the sample sizes might not have been large enough for detection of this AE.¹⁷

Febrile seizure may or may not be causally associated with TIV. The data presented in this report are only to generate hypotheses, because of the multiple limitations of passive surveillance data discussed above. However, febrile seizures among infants have been found to be associated with some childhood vaccines.³⁶ Barlow et al³⁷ found an attributable risk of febrile seizures of 6 to 9 cases per 100 000 subjects

after administration of diphtheria-tetanus-pertussis vaccine (which was subsequently replaced with diphtheria-tetanus-acellular pertussis vaccine, which is apparently associated with fewer AEs than diphtheria-tetanus-pertussis vaccine). Barlow et al³⁷ found no long-term sequelae from febrile seizures after either diphtheria-tetanus-pertussis vaccine or measles-mumps-rubella vaccine administration, which is important because of potential implications for other vaccines that may trigger febrile seizures, such as TIV. Blumberg et al³⁸ assessed the risk factors for AEs after diphtheria-tetanus-pertussis vaccine administration and reported high rates of personal and family histories of seizures among seizure patients, 90% of whom had documented fevers (temperature of $\geq 38^{\circ}\text{C}$). In a population-based, case-control study with 424 confirmed cases, Gale et al³⁹ found that rates of serious acute neurologic illnesses (including complex febrile seizures and seizures without fever) were not statistically significantly increased among diphtheria-tetanus-pertussis vaccine recipients, compared with control subjects.

Fever after TIV, whether causally related to the vaccine or not, was associated with most reported seizures among children <2 years of age who received TIV. An association between TIV and nonfebrile seizures among infants cannot be excluded without a large controlled study, but the number of these reports in the VAERS database was small ($N = 8$) and their presence was not unexpected, because of the coincidental occurrence of the disorder in this age group.⁴⁰ In addition, the Vaccine Safety Datalink study comparing the periods before and after vaccination with TIV among children found no increase in seizures after vaccination.⁸ In VAERS, no personal or family history of seizures was reported for most of the patients with febrile or nonfebrile seizures, although family history data might have been incompletely reported.

Reports of children <6 months of age who experienced an AE after TIV administration suggest that this vaccine is being used outside the recommended age range for some infants. The number of instances of deviation from this recommendation cannot be determined from these data. The patterns of the severity of events do not appear to differ between the <6-month-old subjects and the 6- to 23-month-old subjects; however, the small number of reports for the younger age group limits the inferences that can be made.

CONCLUSIONS

The number of TIV-related VAERS reports for children <2 years of age increased in the post-ACIP guideline period, probably because of an increase in the number of vaccinees after the ACIP announcement. A direct comparison of AE reporting in the pre-ACIP guideline and post-ACIP guideline periods is confounded by the fact that the vaccinated groups likely differ (with the post-ACIP guideline group having a lower prevalence of underlying health conditions). VAERS is a passive surveillance system, with all of the limitations mentioned above. It is particularly important to remember that the relative

frequency of reporting of AEs may or may not bear any resemblance to the relative incidence of these events, as might be determined with an active surveillance system or a clinical trial. Nonetheless, the safety profiles in the pre-ACIP guideline and post-ACIP guideline periods appeared similar. Of note, large proportions (although a relatively small absolute number) of serious and overall reports after TIV administration among <2-year-old subjects described seizure. Febrile seizures are common among subjects 6 months to 2 years of age, may be related to any fever-inducing stimulus, and have not been found to result in serious sequelae.³⁹ Additional postlicensure studies might be valuable in characterizing rates of seizures after pediatric influenza vaccine administration. In accordance with the Institute of Medicine recommendation for enhanced surveillance of neurologic AEs after vaccination,¹³ the Centers for Disease Control and Prevention and the Food and Drug Administration are working to promote such reporting.^{41,42}

This study provides generally reassuring, although limited, data regarding the safety of TIV among infants and toddlers, which is an important consideration in light of the ACIP recommendation. Continued surveillance for seizures and other events of concern is warranted and will continue.

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ARE DOLLS, BLOCKS, AND STUFFED ANIMALS FADING AWAY, AND IS CHILDHOOD FADING WITH THEM?

“Whatever happened to toys? Real toys, like dolls and model airplanes? A recent Kaiser Family Foundation survey found that half of all 4- to 6-year-olds have played video games, a quarter of them regularly. Game makers are aggressively marketing to children as young as 3, while researchers report what parents already know: that children as young as 8 and 9 are asking for adult toys, like cell phones and iPods, rather than stuffed animals or toy trucks. The trend has squeezed both makers and sellers of traditional toys, from the electric train company Lionel to retailers like Toys ‘R’ Us and FAO Schwarz. ‘I have seen 1-year-olds wanting to play with their parents cellphones,’ said Irma Zandl of the Zandl Group, a youth-marketing research company. And they know the difference, she said, between a real and a fake one. Which raises a question: As toys change, has play itself fundamentally changed? For that matter, does the early attachment to grown-up toys in some way shorten in the imaginative world of childhood, with its pretend tea parties and make-believe cops and robbers? ‘The span in which children play with certain kinds of toys certainly has shrunk,’ said Dr Gary Cross, a historian in Pennsylvania State University and author of *The Cute and the Cool*, an analysis of children’s consumer culture. ‘It used to be that 14-year-old girls could still play with dolls, and 14-year-old boys would still get Erector Sets as gifts.’ Young children who have active imaginary lives tend to be adept reasoning about unknown situations and taking on another’s perspective, studies suggest. ‘I think there are deep continuities between the functioning of the imagination in early childhood and its functioning later,’ Dr Paul L. Harris, a psychologist at Harvard and author of *The Work of the Imagination*. . . . The increasing use of electronic toys troubles Dr Jerome L. Singer, a professor emeritus of psychology at Yale. ‘One thing we know is that kids in preschool years need to be in touch with the real world.’ He said. ‘No matter how brilliant they are, they’re not going to learn to walk, to move, to interact with others unless their hands or feet have a direct role in such activity. Plopping kids in front of a TV or computer cuts away a whole aspect of that development.’ . . . [In] a 2001 survey of 1800 children aged 5 to 12, British researchers found that more than 45 percent had an imaginary companion at some point in their lives, a much higher rate than the authors expected. Imaginary friends, believed by some researchers to foster the development of empathy and sociability, typically are not based on toys, and have more social dimension than would be provided by a game character, a recent analysis found.”

Carey B. *New York Times*. November 28, 2004

Noted by JFL, MD

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

Ann W. McMahon, John Iskander, Penina Haber, Soju Chang, E. Jane Woo, M. Miles Braun and Robert Ball

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