Safety of Trivalent Inactivated Influenza Vaccine in Children Aged 24 to 59 Months in the Vaccine Safety Datalink

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Objectives: To evaluate the safety of trivalent inactivated influenza vaccine (TIV) in children aged 24 to 59 months and to evaluate the risk of medically attended events (MAEs) in a subcohort of children who had multiple annual doses of TIV over their lifetimes.

Design: Self-controlled screening study.


Participants: Children aged 24 to 59 months who received at least 1 TIV dose (66,283 children and 91,692 TIV doses).

Exposure: Vaccination with TIV.

Main Outcome Measures: Medically attended events in inpatient and emergency department settings in one of the following risk windows: 0 to 2, 1 to 14, or 1 to 42 days after vaccination. All MAEs that met the screening criteria of incidence rate ratios (IRRs) exceeding 1.0 and \( P < .05 \) or IRRs exceeding 2.0 and \( P < .20 \) underwent medical record review. A secondary analysis examined the risk of MAEs in children who had multiple annual lifetime TIV doses.

Results: Nine diagnoses met the screening criteria. After medical record review, gastrointestinal tract symptoms (IRR, 1.18; 95% confidence interval [CI], 1.10-1.25), gastrointestinal tract disorders (7.70; 1.11-53.52), and fever (1.71; 1.64-1.80) remained significantly associated with vaccination. None of the events seemed to be serious, and none had complications. In the secondary analysis, there was an apparent dose response for vaccine and allergic reactions in the 1- to 3-day risk window.

Conclusions: There was no evidence of serious MAEs following vaccination with TIV among children aged 24 to 59 months. Further studies are warranted to evaluate the risk of MAEs in children with multiple lifetime TIV doses.


THE POPULATION OF CHILDREN for whom annual influenza vaccination is recommended has expanded over the last decade. In 2004, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommended the trivalent inactivated influenza vaccine (TIV) for all healthy children aged 6 to 23 months. Annual influenza vaccination was then recommended in 2006 for children aged 24 to 59 months and in 2008 for children aged 6 months to 18 years. Unlike vaccine effectiveness, safety cannot be measured directly and must be inferred from the relative absence of vaccine adverse events. Large postmarketing studies have an important role in detecting rare and serious vaccine adverse events that may have been missed in prelicensure clinical trials. Although TIV has a good record of safety, only 2 large postmarketing studies have evaluated the safety of TIV in children: the first study focused on all children younger than 18 years but was conducted well before the expanded recommendations, and the second study evaluated safety only in children aged 6 to 23 months. Therefore, safety data specific to a large population of children aged 24 to 59 months are lacking. Moreover, little is known about the safety of TIV among children who receive multiple annual doses over their lifetimes. This latter question is of particular interest to the Advisory Committee on Immunization Practices.

The primary objective of this study was to evaluate the safety of TIV in children...
aged 24 to 59 months. We screened a large cohort of children from 7 US managed care organizations (MCOs) for evidence of increased risk of medically attended events (MAEs) following vaccination with TIV. We also evaluated the risk of MAEs in a subcohort of children who had multiple annual doses of TIV over their lifetimes.

**METHODS**

**STUDY DESIGN AND SETTING**

In a cohort of children aged 24 to 59 months, we conducted a self-controlled screening analysis to examine the risk of MAEs following vaccination with TIV. The setting for this study was the Vaccine Safety Datalink, a collaborative project between the Centers for Disease Control and Prevention and 8 MCOs across the United States. The 8 participating MCOs comprise a population of more than 9 million members annually (3% of the US population). Seven of 8 MCOs contributed data to the analyses, and each site's institutional review board approved the study.

**STUDY POPULATION AND MAEs**

We examined 4 influenza seasons from October 1, 2002, to March 31, 2006. The study cohort included children aged 24 to 59 months who received at least 1 TIV dose during the study period. Each vaccinated child had to be continuously enrolled in his or her respective MCO for a minimum of 1 influenza season. Children could be in the analyses more than once if they were vaccinated in more than 1 season. Multiple annual vaccinations in the same child were analyzed as independent exposures.

An extensive list of potential MAEs was compiled a priori through a systematic literature review. We chose biologically plausible or serious conditions that were observed in prior post-marketing safety studies, passive surveillance, or clinical trials. Medically attended events were defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. We used 237 ICD-9-CM codes; 206 codes were combined into 24 groupings of clinically related codes, and 31 codes were evaluated individually. These codes represented conditions such as fever, limb soreness, allergic reactions, cardiac events, hypotension, gastrointestinal (GI) tract symptoms (vomiting and diarrhea), GI tract disorders (appendicitis and intestinal obstruction), febrile seizures, and nervous system disorders (peripheral autonomic neuropathy and mononeuropathy of the limbs). The complete list of codes is available from the corresponding author.

**DATA ANALYSES**

**Primary Analyses**

We used a self-controlled case series (SCCS) analysis to examine the temporal relationship between TIV and the incidence of MAEs. In an SCCS analysis, the incidence rate of events in postvaccination risk windows is compared with the incidence rate in unexposed periods before and after the risk windows. Only individuals who experience the event of interest are included in the analysis, and each individual acts as his or her own control. Because individuals are compared with themselves, the SCCS method implicitly controls for unmeasured confounding variables that do not vary over time, such as sex, race/ethnicity, and chronic health disorders. The SCCS method is an efficient and valid alternative to more traditional epidemiologic study methods, such as the cohort and case-control for evaluating the safety of vaccines.

In the cohort of vaccinated children, separate SCCS analyses were conducted for each MAE in one of the following predefined risk windows: 0 to 2, 1 to 14, or 1 to 42 days after vaccination. Within a given influenza season, follow-up time in the risk window represented exposed person-time, and all the follow-up time before and after the risk window represented unexposed person-time. For the 0- to 2-day risk window, we focused on acute reactions, such as rash, fever, cellulitis, limb soreness, seizures, and allergic reactions. The 1- to 42-day risk window was primarily used for diagnoses with delayed onset, such as Guillain-Barré syndrome (GBS). A combination of conditions with acute and delayed onsets was examined in the 1- to 14-day risk window. We only examined MAEs that occurred in inpatient and emergency department settings. Outpatient data were not used because their inclusion has been associated with a high rate of false-positive signals in prior vaccine safety studies. Moreover, we were interested in potentially serious MAEs that led to an emergency department visit or hospitalization. In a separate set of analyses, we examined if the risk of MAEs after vaccination with TIV was different in a cohort of children with a medical condition that places them at high risk for influenza-associated morbidity.

Conditional Poisson regression analysis was used to estimate incidence rate ratios (IRRs), with adjustment for calendar month and age. We excluded the 14 days immediately preceding vaccination from the analyses because this time may represent a period when children are most likely to be healthy (the healthy vaccinee effect) and may underestimate the true background rate of MAEs. Only the first occurrence of an MAE in an unexposed or risk window was analyzed.

Signals for MAEs in the analyses of electronic MCO data were validated by a medical record review. Specifically, a medical record review was conducted using the following a priori screening criteria: MAEs with IRRs exceeding 1.0 and \( P < 0.05 \) or IRRs exceeding 2.0 and \( P < 0.20 \). For each MAE, participating sites copied the medical records for the entire influenza season of interest. Copied records were deidentified and sent to the lead site for review. At the lead site, 2 trained medical record abstractors (K.J.N. and another colleague), blinded to vaccination status, verified the electronically identified medical encounter date and the visit diagnosis and determined if the MAE of interest was an incident case or worsening of a preexisting condition. Abstractors further determined whether the MAE was clearly attributed to another cause (eg, limb soreness due to blunt trauma). Last, abstractors recorded presenting symptoms, underlying chronic conditions, laboratory results, or any other information relevant to the diagnosis. A clinical investigator (M.F.D.) reviewed a sample of records for all signals and resolved any discrepancies between the abstractors. At the conclusion of the medical record review, medical record–confirmed cases were reanalyzed using conditional Poisson regression to determine if the significant \( P \leq 0.05 \) association remained.

A random sample of medical records was reviewed for less serious and common conditions (>300 events) that generated a positive signal. Results from this sample medical record review were used to estimate the proportion of confirmed MAEs in the exposed and unexposed windows. In a simulation analysis, these proportions were then applied to the electronic MAEs and replicated 1000 times to generate a distribution of IRR estimates for each condition. The median IRR for each distribution was calculated.

**Secondary Analyses**

A stratified SCCS analysis examined the risk of MAEs in children who had multiple lifetime TIV doses. Each stratum was limited to vaccinated children who received 1, 2, 3, 4, or 5 life-
time TIV doses. Only doses administered between October 1, 2002, and March 31, 2006, were analyzed. Separate IRR estimates were generated for each dose stratum, controlling for age and season. Despite their limitations, outpatient data were included in this multiple-dose analysis because of the anticipated rarity of events across subsequent doses. Dose-specific IRR estimates were calculated for risk windows of 1 to 3, 1 to 14, or 1 to 42 days following the most recent annual TIV dose received. We excluded day 0 (the vaccination date) from the 3-day risk window because it has been shown that inclusion of outpatient data on day 0 leads to high rates of spurious signals. A subset of 24 individual ICD-9-CM codes and 5 aggregated codes from the primary analyses were examined. These codes represented acute outcomes and conditions with delayed onsets, including rash, fever, limb soreness, vaccine and allergic reactions, and GBS. A medical record review was conducted on MAEs with IRRs exceeding 1.0 and $P \leq .05$ or IRRs exceeding 2.0 and $P < .20$, and with IRRs that seemed to increase with TIV dose. The medical record review process was similar to that for the primary analyses. Process flowcharts are available from the corresponding author.

RESULTS

PRIMARY ANALYSES

The overall study cohort included 66,283 children aged 24 to 59 months, who received 91,692 TIV vaccinations between October 1, 2002, and March 31, 2006. The sex distribution in the cohort was approximately equal (47.4% female), with a mean age at vaccination of 2.9 years (Table 1). Approximately 4% ($n=2584$) of children were at high risk for influenza-associated morbidity.

In the primary analyses, there were 12,399 emergency department visits and 4,492 hospitalizations among the cohort (Table 1). These data generated 142 conditional Poisson regression models, 38 (26.8%) of which had an IRR exceeding 1.0. Nine associations (6.3%) met the screening criteria and were explored further with a secondary analysis (Table 2). This single statistically significant association was with aggregated GI tract disorder, and nervous system disorder met the screening criteria within the subcohort of children with high-risk medical conditions. The other 4 conditions—rash, fever, limb soreness, and GI tract symptoms (vomiting and diarrhea)—were more common and potentially less serious.

For the 5 potentially serious conditions, 67 MAEs underwent medical record review, and 47 (70.1%) were excluded from final analyses. Detailed reasons for these exclusions are given in Table 3. When the data were restricted to medical record–confirmed events, 1 association remained statistically significant and 4 associations were nonsignificant (Table 2). This single statistically significant association was with aggregated GI tract disorders in children with a high-risk health condition (IRR, 7.70; 95% confidence interval [CI], 1.11-53.52). Six of 7 confirmed cases in this final analysis presented with adult abdominal pain of unknown cause; none had documented intestinal tract obstruction.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total influenza vaccinations</td>
<td>91692</td>
</tr>
<tr>
<td>Age at vaccination, mean (SD), y</td>
<td>2.9 (0.8)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>31447 (47.4)</td>
</tr>
<tr>
<td>With high-risk health condition, No. (%)</td>
<td>2584 (3.9)</td>
</tr>
<tr>
<td>No. of hospitalizations analyzed</td>
<td>4492</td>
</tr>
<tr>
<td>No. of emergency department visits analyzed</td>
<td>12399</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the Study Cohorts, 2002 Through 2006 Influenza Seasons

The medical records of 138 patients were reviewed for the following 4 potentially less serious conditions: rash ($n=30$), limb soreness ($n=32$), fever ($n=38$), and GI tract symptoms (vomiting and diarrhea) ($n=38$). The number of medical records reviewed for fever and GI tract symptoms represents a 10% random sample of each condition. For rash, 6 events were excluded on medical record review for the following reasons: existing conditions ($n=4$), unavailable medical records ($n=1$), and no encounter located in medical records ($n=1$). Reanalysis of confirmed rash-related events ($n=24$) generated a non-significant IRR. For limb soreness, 5 events were excluded for the following reasons: unavailable medical records ($n=3$), incorrect diagnosis date ($n=1$), and no encounter located in medical records ($n=1$). Of the remaining 27 events, 26 were attributed to other causes, including trauma ($n=25$), and Lyme disease ($n=1$). The remaining patient with limb soreness presented to the emergency department with itchiness and redness after vaccination with TIV; reanalysis with this single case resulted in a statistically significant ($P = .04$) association. Review of randomly selected medical records containing codes for fever and for GI tract symptoms suggested that most events could not be attributed to a known cause and should remain in the final analysis. Of 76 medical records, 46 (60.5%) were confirmed events. Reasons for
exclusion included diarrhea due to other causes (eg, antibiotics) (n=8), no encounter located in medical records (n=8), fever attributed to another cause (eg, pneumonia) (n=6), unavailable medical records (n=5), condition not confirmed in medical records (n=2), and preexisting chronic nausea (n=1). In the simulation analyses of confirmed events, estimated IRRs for fever and for GI tract symptoms exceeded 1.0 and were statistically significant (Table 2).

SECONDARY ANALYSES

Among children with multiple annual doses of TIV, there was an apparent dose response for vaccine and allergic reactions in the electronic analyses for the 1- to 3-day risk window (Table 4). The respective IRRs for the second through the fifth doses increased incrementally from 6.19 to 16.45 and were statistically significant. A total of 74 medical records were reviewed, 57 (77.0%) of which were excluded. Reanalysis with confirmed events showed IRRs of 55.15 for the second dose, 49.33 for the third dose, and 213.33 for the fourth dose. The association with the fifth dose was statistically significant (P=.04), but an IRR could not be calculated because there was only 1 exposed case and no unexposed cases. Differences between the magnitudes of the dose-specific IRRs were not statistically significant.

We screened a large cohort of children aged 24 to 59 months to identify signals for potential adverse events following vaccination with TIV. The study cohort comprised 91 692 unique vaccinations, representing 66 283 children across 7 MCOs. In the primary analyses, we analyzed 142 potential associations, 4 of which remained statistically significant after medical record review. We found no evidence of any serious adverse MAEs in TIV postvaccination risk windows of 0 to 2, 1 to 14, or 1 to 42 days.

Of 4 associations that were confirmed after medical record review, fever and limb soreness represent commonly reported adverse events of vaccination.\textsuperscript{8,9,15,23} None of the events seemed to be serious, and none had complications. Furthermore, the final analysis with limb soreness had only 1 event. Although we do not believe that these signals warrant further investigation, they provide reassurance that our methods were sensitive enough to detect associations with common vaccine adverse events.
The signals for GI tract disorders (in children with high-risk medical conditions) and for GI tract symptoms (vomiting and diarrhea) may represent true reactions to TIV. For both signals, most cases after medical record review were nonserious acute episodes of vomiting, diarrhea, or abdominal pain. Similar associations were seen in a previous TIV screening study of children aged 6 to 23 months. As noted in the previous study, it is possible that events occurring in the risk period represent children who were exposed to GI tract viruses in their physicians' offices when waiting to get vaccinated with TIV.

An apparent dose-response relationship was observed in the electronic analysis for vaccine and allergic reactions in the 1- to 3-day risk window. Biologically, it is possible that certain subpopulations become susceptible to vaccine reactions after multiple annual exposures. For example, with diphtheria, tetanus, and pertussis vaccination, the fifth booster dose between ages 4 and 6 may represent a higher risk because of cumulative exposure. The signals for GI tract disorders (in children with high-risk medical conditions) and for GI tract symptoms (vomiting and diarrhea) may represent true reactions to TIV. For both signals, most cases after medical record review were nonserious acute episodes of vomiting, diarrhea, or abdominal pain. Similar associations were seen in a previous TIV screening study of children aged 6 to 23 months. As noted in the previous study, it is possible that events occurring in the risk period represent children who were exposed to GI tract viruses in their physicians' offices when waiting to get vaccinated with TIV.

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and 6 years is associated with whole-limb redness or swelling in approximately 1% to 2% of vaccine recipients. In our screening analysis, the risk for vaccine and allergic reactions increased incrementally following the second through the fifth annual doses of TIV. In analyses limited to medical record–confirmed cases, the associations were greater in magnitude, but there were fewer events, the confidence intervals widened, and the dose-response relationship became less distinct. Now that influenza vaccination is universally recommended for all ages, these associations warrant further study in a larger population across a wider age range. Future research should also focus on developing analytic methods to measure cumulative risk when there are multiple annual exposures and events across the lifetime.

This study has several limitations. To maximize the likelihood of detecting important safety signals, we examined numerous associations, increasing the likelihood that statistically significant signals may have surfaced by chance alone (type I error). In addition, our analyses were based on MCO administrative data that are not collected for research purposes, and it is possible that many of the MAEs were misclassified and did not represent true incident cases. However, several steps were taken to minimize these potential sources of error and bias. First, outpatient data were not included in the primary analyses because it has been shown that such data are associated with a high rate of false-positive signals and significant misclassification. Second, only carefully chosen prespecified conditions were analyzed as potential vaccine adverse events. Prior TIV screening studies used data-mining techniques to identify unanticipated signals, but the analyses produced numerous statistically significant associations that were not medically plausible, including obesity, insect bites, and joint sprains. Third, all positive signals were validated with a rigorous medical record review. This last step excluded a large proportion of the electronic MAEs (46.2%) from the final analysis because they represented prevalent cases or conditions with a clear cause. The review also showed that some of the medical records were missing and that a small proportion of the MAEs could not be confirmed in the medical records. We believe that these 3 steps increased the validity of our results and decreased the likelihood of type I error. These results also highlight the importance of conducting medical record review to validate potential safety signals that arise in observational studies of vaccine safety.

Despite our large cohort size, it is possible that our study missed rare potential adverse events. For example, GBS has been a suspected adverse event of influenza vaccination since the 1976 influenza A(H1N1) epidemic, and it continues to be reported to the Vaccine Adverse Event Reporting System. Acute idiopathic polyneuritis occurs approximately once per every million doses of vaccine administered, and there were no cases in our entire cohort. Efforts to monitor the risk of GBS following influenza vaccination in children and adults are ongoing in the Vaccine Safety Datalink.

To our knowledge, this investigation represents the largest TIV screening study for children aged 24 to 59 months to date. After medical record review, 4 acute non-serious conditions seemed to be temporally related to TIV vaccination. Two are known minor adverse events (fever and limb soreness), and 2 likely represent the same condition (GI tract disorders and GI tract symptoms [vomiting and diarrhea]) that has been identified in prior TIV safety research. Therefore, our results provide additional evidence that TIV is safe in young children.

Accepted for Publication: February 18, 2011.

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Author Contributions: Dr Glanz had full access to all 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: Glanz, Hambridge, Daley, Narwaney, Xu, and Nordin. Acquisition of data: Glanz, Newcomer, Narwaney, Baggs, Klein, Naleway, and Weintraub. Analysis and interpretation of data: Glanz, Newcomer, Hambridge, Daley, Xu, Lee, Nordin, Belongia, and Weintraub. Drafting of the manuscript: Glanz, Newcomer, Daley, and Weintraub. Critical revision of the manuscript for important intellectual content: Glanz, Newcomer, Hambridge, Daley, Narwaney, Xu, Lee, Baggs, Klein, Nordin, Naleway, Belongia, and Weintraub. Statistical analysis: Glanz, Newcomer, and Baggs. Obtained funding: Glanz, Hambridge, and Klein. Administrative, technical, and material support: Narwaney, Baggs, and Weintraub. Study supervision: Glanz, Hambridge, Daley, and Klein.

Financial Disclosure: None reported.

Funding/Support: This study was funded through a subcontract with America’s Health Insurance Plans under contract 200-2002-00732 from the Centers for Disease Control and Prevention.

Disclaimer: The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Previous Presentation: Preliminary findings of this study were presented at the Annual Meeting of the
Pediatric Academic Societies; May 2, 2009; Baltimore, Maryland.

Additional Contributions: Jo Ann Shoup, MS, and Kate Burniece, BS, assisted with project management and medical record abstraction. Lisa Jackson, MD, MPH, provided input on an earlier version of the manuscript. We thank the data management and medical record abstraction staff at each of the participating sites for their valuable work in creating the Vaccine Safety Datalink data sets and for their review of medical records.

REFERENCES


