Febrile Seizures Associated with Trivalent Influenza Vaccine and 13-Valent Pneumococcal Vaccine 2010-2011 Season

Decision Making by the ACIP General Recommendations Working Group
Subgroup on Febrile Seizures

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Public Health – Seattle & King County
Professor in Medicine, University of Washington
Febrile Seizure Signal Detection

- April 2010, Australia: Increase in febrile seizures 0-1 days after vaccination of children <5 years with CSL trivalent inactivated influenza vaccine, not seen with other influenza vaccine products
- ACIP recommended not using CSL vaccine for children 6 months – 8 years in the US; vaccine was not distributed in the US; FDA added label warning
- Previous evaluations in US (different formulations) did not show elevated risk of seizures in 0-7, 0-2, or 1-3 days following influenza vaccination
Febrile Seizure Signal Detection
Enhanced monitoring in US

• November, 2011: VAERS enhanced surveillance detects increase in febrile seizure reports after trivalent influenza vaccine (TIV) administration; most in children 6-23 months
• In US, Fluzone® only TIV product administered to children 6-23 months during the 2010-2011 season
• Vaccine Safety Datalink (VSD) revises risk interval to 0-1 days after vaccination for surveillance for seizures
  • Signal for seizures detected in November, 2011 in 6-59 month old children
  • Subsequent evaluations to evaluate whether signal represented true increase in risk
  • Febrile seizures appeared associated with receipt of TIV and pneumococcal conjugate vaccine (PCV13)
Febrile Seizure Signal Detection
Enhanced monitoring in US

• FDA and CDC Announcements on Fluzone® and febrile seizures
  • Update on Fluzone® Influenza Vaccine and VAERS Reports of Febrile Seizures in Children (January 20, 2011)
  • Update: Vaccine Adverse Events reporting System (VAERS) Data on Febrile Seizures after Vaccination with Fluzone®, a 2010-2011 Trivalent Inactivated Vaccine, in Children (January 21, 2011)


DeStefano, ACIP FEB 2011
ACIP General Recommendations Working Group
Febrile Seizure Subgroup

• Charge (March 2011):
  – Review data on the risk for febrile seizures after seasonal trivalent inactivated influenza vaccine (TIV) and pneumococcal conjugate vaccine (PCV) in children
  – Present options to ACIP for any action(s) related to the use of these vaccines for the 2011-12 influenza season
  – Provide a framework for determining when vaccine-associated febrile seizures should lead to a change in recommendations for administration of one or more vaccines
General Recommendations Working Group
Subgroup on Febrile Seizures

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Febrile Seizures

Background

- Seizures that occur in febrile children that do not have intracranial infection, metabolic disturbance or history of afebrile seizures
  - Typically occurs at 6-60 months; peak: 14-18 months
- Affects 2-5% of children in the US
- Generally excellent prognosis, few sequelae
- 1/3 with first febrile seizure will have recurrence
- Fever reducing medications have not been shown to prevent febrile seizures
Febrile Seizures and Vaccines
Background

- Fever following vaccination can potentially increase risk for febrile seizures in children
- Known associations with febrile seizures and whole cell pertussis vaccine and measles-containing vaccines
- Attributable risk
  - DTwP: 6-9/100,000 doses
  - MMR: 24-156/100,000 doses
  - MMR-V: 38-43/100,000 doses
  - DTaP NOT associated with increased risk for febrile seizures


DeStefano, ACIP FEB 2011
ACIP Recommendations for Influenza Vaccination for Children Aged ≥6 Months

• Annual vaccination recommended for all persons ≥6 months
  - For some children 6 mo. through 8 yrs receiving seasonal influenza vaccine for the first time, two doses are required to ensure adequate immune response
  - Doses must be administered a minimum of 4 weeks apart

• Schedule determined to some extent by time of year (vaccine becomes available approximately in September)
  - Optimal protection afforded by administration of both doses early in season

MMWR 2010;59:1-62
ACIP Recommendations for Pneumococcal Conjugate Vaccine (PCV13)

- For routine immunization of infants, PCV13 is recommended as a 4-dose series at ages 2, 4, 6, and 12--15 months
  - 2010 recommendation for PCV13 superseded 2000 ACIP recommendation for PCV7
  - 2010-11 first season with PCV13 in widespread use
Febrile Seizures Signal in the Vaccine Safety Datalink (VSD) Harvard Pilgrim Health Care Institute, Southern California Kaiser Permanente, Centers for Disease Control and Prevention

- Presented preliminary findings at February and June 2011 ACIP meetings
- Methods and results published in February, 2012
  - Tse et al. Vaccine 2012; 30:2024-2031
Vaccine Safety Datalink (VSD) Project

- Collaboration between CDC and 10 managed care organizations
- Data on 9.2 million persons
  - 2.2 million children
  - 7 million adults
  - \(\sim3\%\) of U.S. population
- VSD Rapid Cycle Analysis (RCA) conducts near real-time surveillance to monitor vaccine safety, particularly for newer vaccines
VSD monitoring for febrile seizures after 2010-11 trivalent inactivated influenza vaccine (TIV)

- VSD monitored 9 outcomes after TIV, including seizures
  - ICD9 code for convulsion (780.3)
  - Inpatient and emergency department setting (High positive predictive value)
- Detected possible increased risk of febrile seizures on days 0-1 post-vaccination among 6-59 mo who received 1st dose of TIV (*signal*)
  - Chart review verified most seizures were febrile
  - Risk appeared higher in 6-23 month old children
  - Most had received other vaccines, most commonly 13-valent pneumococcal conjugate vaccine (PCV13) and DTaP
  - Re-evaluation of data from past seasons using 0-1 day interval did not show similar elevation in risk for seizures
  - No increase in risk of seizures following monovalent H1N1 vaccine in 2009-2010 season

Lee, Tokars, ACIP February, June 2011
Study Design for Seizures

- Self controlled design was identified as **primary** approach (binomial maxSPRT) for seizures

![Graph showing two risk windows: one for vaccine (current) and another for vaccine (historical).]

- Current vs. historical (2005-06 to 2009-10 TIV vaccinees) identified as **alternative** approach (Poisson or CmaxSPRT)

Lee, ACIP June 2011
## SCD Across Multiple Seasons, 6-59 months

<table>
<thead>
<tr>
<th>Flu season</th>
<th>Vaccine</th>
<th>Risk Window (0-1)</th>
<th>Comparison Window (14-20)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-06</td>
<td>TIV</td>
<td>9</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>2006-07</td>
<td>TIV</td>
<td>13</td>
<td>26</td>
<td>1.8</td>
</tr>
<tr>
<td>2007-08</td>
<td>TIV</td>
<td>4</td>
<td>23</td>
<td>0.6</td>
</tr>
<tr>
<td>2008-09</td>
<td>TIV</td>
<td>13</td>
<td>23</td>
<td>2.0</td>
</tr>
<tr>
<td>2009-10</td>
<td>TIV</td>
<td>9</td>
<td>27</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>TIV</td>
<td><strong>48</strong></td>
<td><strong>115</strong></td>
<td><strong>1.5 (1.02, 2.0)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flu season</th>
<th>Vaccine</th>
<th>RW (0-1)</th>
<th>CW (14-15)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2010</td>
<td>MIV</td>
<td>5</td>
<td>6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flu season</th>
<th>Vaccine</th>
<th>RW (0-1)</th>
<th>CW (14-20)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-11**</td>
<td>TIV</td>
<td>23</td>
<td>21</td>
<td>3.8 (2.1, 6.9)</td>
</tr>
</tbody>
</table>

** Based on available data on influenza vaccines given through 01/29/11 Lee, ACIP FEB 2011.
# SCD Stratified by Age, Gender (ICD9 Data)

<table>
<thead>
<tr>
<th>Age group*</th>
<th>RW (0-1)</th>
<th>CW (14-20)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-23 mo</td>
<td>20</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>24-59 mo</td>
<td>3</td>
<td>7</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
<td><strong>21</strong></td>
<td><strong>3.8</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender*</th>
<th>RW (0-1)</th>
<th>CW (14-20)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>8</td>
<td>10</td>
<td>2.8</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>11</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
<td><strong>21</strong></td>
<td><strong>3.8</strong></td>
</tr>
</tbody>
</table>

* Based on available data on influenza vaccines given through 01/29/11
Concomitant Vaccines among Cases and Vaccinees 6-23 months, 2010-11

- Seizure cases (N=20)
  - The majority concomitantly received either PCV13 (75%) and/or DTaP-containing vaccines (65%)
  - 11 children received both PCV13 and DTaP-containing vaccines
  - Only 15% of seizure cases received TIV only (i.e. no concomitant vaccines given)

- TIV vaccinees (N=77,338)
  - Fewer TIV vaccine recipients concomitantly received PCV13 (36%) and/or DTaP-containing vaccines (34%)
  - 44% received TIV only

- Of note, many children received both PCV13 and DTaP simultaneously with TIV, but only PCV13 was new this season

Lee, ACIP FEB 2011
## Concomitant Vaccines among Cases (N=20) and Vaccinees 6-23 months (N=77,338), 2010-11

<table>
<thead>
<tr>
<th>Concomitant vaccines</th>
<th>Seizure Cases (N=20)</th>
<th>TIV Vaccinees (N=77,338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13*</td>
<td>15 (75%)</td>
<td>27,648 (36%)</td>
</tr>
<tr>
<td>DTaP* (4 cases received combo vaccines)</td>
<td>13 (65%)</td>
<td>26,420 (34%)</td>
</tr>
<tr>
<td>Hib</td>
<td>8 (40%)</td>
<td>23,607 (31%)</td>
</tr>
<tr>
<td>MMR</td>
<td>7 (35%)</td>
<td>11,470 (15%)</td>
</tr>
<tr>
<td>Varicella</td>
<td>7 (35%)</td>
<td>11,191 (15%)</td>
</tr>
<tr>
<td>Hep A</td>
<td>7 (35%)</td>
<td>15,612 (20%)</td>
</tr>
<tr>
<td>IPV (4 cases received combo vaccines)</td>
<td>4 (20%)</td>
<td>16,339 (21%)</td>
</tr>
<tr>
<td>Hep B (4 cases received combo vaccines)</td>
<td>4 (20%)</td>
<td>13,698 (18%)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>3 (15%)</td>
<td>10,975 (14%)</td>
</tr>
<tr>
<td>None (TIV only)</td>
<td>3 (15%)</td>
<td>33,973 (44%)</td>
</tr>
</tbody>
</table>

*11 seizure cases and 20,114 TIV vaccinees received PCV13 +DTaP; all concomitant vaccines were +/- others*
### SCD Stratified by Concomitant PCV13, 6-23 months (ICD9 Data)

<table>
<thead>
<tr>
<th>Concomitant Vaccines*</th>
<th>RW (0-1)</th>
<th>CW (14-20)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza, no PCV13 +/- other vaccine</td>
<td>5</td>
<td>7</td>
<td>2.5 (0.9, 7.5)</td>
</tr>
<tr>
<td>Influenza + PCV13 +/- other vaccines</td>
<td>15</td>
<td>7</td>
<td>7.5 (3.2, 17.9)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>14</td>
<td>5.0 (2.6, 9.8)</td>
</tr>
</tbody>
</table>

* Based on available data on influenza vaccines given through 01/29/11
Joint Signal Evaluation for TIV and PCV-13

• Harvard Pilgrim Healthcare Institute, Southern California Kaiser, CDC

• Evaluate
  – Influenza (+/- other vaccines)
  – Influenza +/- PCV-13 (+/- other vaccines)
  – PCV-13 (+/- other vaccines)

Lee, ACIP FEB 2011
Joint Signal Evaluation

- Design: Self-controlled
- Seizures definition harmonized for influenza and PCV13 protocols:
  - Age group: 6-11mo; 12-23 mo; 24-59 mo
  - ICD9 codes: 780.3*
  - Setting: Inpt, ED
  - Risk window: 0-1 d
  - Comparison window: 14-20 d
  - First in 42 days
Attributable Risk per 100,000, 6-11 mo

Lee, ACIP FEB 2011

* +/- other non-TIV, non-PCV vaccines; assuming chart confirmation rate of 80%
Attributable Risk per 100,000, 12-23 mo

08/05 - 04/10

05/10 - 01/11

(~1 excess febrile seizure in 1640 vaccinees)

PCV7*  TIV+PCV7*  TIV*  PCV13*  TIV + PCV13*  TIV*

* +/- other non-TIV, non-PCV vaccines; assuming chart confirmation rate of 80%

Lee, ACIP FEB 2011
Attributable Risk per 100,000, 24-59 mo

08/05 - 04/10

05/10 - 01/11

PCV7*
TIV+PCV7*
TIV*

PCV13*
TIV + PCV13*
TIV*

* +/- other non-TIV, non-PCV vaccines; assuming chart confirmation rate of 80%
Updated Attributable Risk of Febrile Seizures by Age Group and Concomitant PCV13

### Cases
- **6-11 months**: Risk 6.02
- **12-23 months**: Risk 9.7
- **24-59 months**: Risk 5.04

### Vaccinees
- **6-11 months**: 20,917
- **12-23 months**: 17,999
- **24-59 months**: 18,281

* Duration 2 days for risk interval vs. 7 days for control interval

**+/- other vaccines**

Tokars. ACIP June 2011
New method for estimating attributable risk
Uses information on baseline risk for seizures by age in months from the entire VSD population (provides more stable estimates), rather than estimating baseline risk from the control period for broad age intervals (where there are fewer cases and more uncertainty about baseline risk estimates despite the broad age interval).
Highlights substantial variation in AR by age in months, which is due to the variability in baseline risk by age in months.
Attributable Risk (AR) estimates for febrile seizures following 1st dose TIV, 2010-11 (Updated AUG 2011)

Risk difference per 100,000 doses

- TIV without concomitant PCV13*
- PCV13 without concomitant TIV*
- Concomitant TIV + PCV13*

45/100,000 (~1 excess febrile seizure in 2222 vaccinees)

^Tse A and Lee G for the VSD
*Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines
VSD Analysis - Comments

- Compares risk of febrile seizure for TIV + PCV13 administered simultaneously to no vaccination, not to TIV and PCV13 given separately.
- Point estimates have wide confidence intervals (small numbers of cases).
Burden of Influenza Among Children in the US

• Complications:
  – Respiratory (pneumonia, sinusitis, otitis media
  – viral and secondary bacterial)
  – Musculoskeletal (myositis, rhabdomyelitis)
  – Cardiac (myo/pericarditis)
  – Neurologic (seizures, encephalopathy, encephalitis)
  – Exacerbations of chronic conditions (asthma, cardiac)
Burden of Influenza Among Children in the US

- Hospitalization and mortality rates vary by season, age group. Hospitalization estimates from 2003/4 - 2007/8:
  - <6 months 90-300 per 100,000/year
  - 6-23 months 30-110 per 100,000/year
  - 2-4 years 20-40 per 100,000/year
- Estimated direct costs of hospitalizations for children <5 years $40-160 million and $60-270 million for ED visits
- Mortality estimates 2003/4 season:
  - <6 months 0.88 per 100,000/year
  - 6-11 months 0.59 per 100,000/year
  - 1 year 0.77 per 100,000/year
  - 2 years 0.35 per 100,000/year

Benefit of Influenza Vaccination

• Number needed to vaccinate to prevent one hospitalization from influenza: 1031 – 3050 (at 50% vaccine efficacy in children 6-23 months of age)
Febrile Seizures After Influenza Infection

- Influenza A associated with 17.6% of 923 hospitalized febrile seizures over 5 years (Chung et al)
- In 1997 and 1998, influenza A accounted for 10.8% and 21.7% of febrile seizure admissions, respectively (35% and 44% during periods of peak flu activity) (Chiu et al)
- 19.5% of children admitted with influenza A developed febrile seizures (Kwong et al)
- Positive seasonal correlation noted between peak influenza activity and febrile seizures (Van Zeijl et al)
- Of 435 children 6 months - 4 years of age hospitalized with lab-confirmed influenza during 4 seasons (2000-2004), 27 (6.2%) had febrile seizure (Newland et al)
- Of 74 children hospitalized with influenza A H1N1, 14 (19%) had neurological complications and 6 (8%) had febrile seizures

U.S. Burden of Pneumococcal Disease Among Children <5 Years of Age (Following Introduction of 7-valent Pneumococcal Conjugate Vaccine)

• 1,050,000 illness episodes
• 1,132,000 antibiotic courses
• 42,000 hospitalizations

Huang, Vaccine 2011;29:3398-412
13-valent Pneumococcal Conjugate Vaccine (PCV13)

- Introduced into routine schedule in March 2010
- Replaced PCV7, which was associated with prevention of 211,000 cases of IPD during 2000-2007 (Pilishvili JID 2010)
- Recommended for all children at 2, 4, 6, and 12-15 months
- Relevance of booster dose in 2\textsuperscript{nd} year of life:
  - Additional individual protection over primary series
  - Likely important for mucosal immunity (pneumonia, otitis)
  - Considered important for reducing transmission to other age groups
Seasonality of Invasive Pneumococcal Disease - Children 12-23 months, 1998-2008

60% of annual IPD cases occur during October-March

CDC, Active Bacterial Core surveillance, unpublished
October 2011 ACIP Meeting
General Recommendations Working Group
Febrile Seizures Subgroup - Assessment

• Significant morbidity of influenza and pneumococcal disease among children
  • Timely vaccination important in preventing seasonal morbidity and mortality for influenza and pneumococcal infections requires
  • Likely benefit of vaccination in preventing febrile seizures due to influenza and pneumococcal infections
  • Potential for missed opportunities if schedule modified
• Although distressing, febrile seizures largely benign
October 2011 ACIP Meeting
General Recommendations Working Group
Febrile Seizures Subgroup - Assessment

- Unclear if risk after simultaneous administration of TIV and PCV13 is greater than with separate administration
- Unclear if association between influenza vaccine and febrile seizures is unique to 2010-2011 vaccine strains
- Cases with concurrent infection not excluded from analysis
- Relatively small numbers of cases
- Further investigation is underway to determine if other vaccines besides TIV and PCV13 may be contributing to the febrile seizures
  - Evaluation of confounding or effect modification by concomitant administration of DTaP with PCV13 or TIV
October 2011 ACIP Meeting
General Recommendations Working Group
Febrile Seizures Subgroup - Conclusions

- Benefits of TIV and PCV13 vaccination >> risk
- Education of healthcare providers and parents on the increased risk of febrile seizures and benefits of TIV and PCV13
- No change in recommendation for simultaneous administration
Update on Febrile Seizures in Children Following Vaccination with Influenza Vaccines and Pneumococcal Vaccines

CDC and the Food and Drug Administration (FDA) continuously monitor the safety of vaccines recommended for children and adults in the United States. Since vaccinations may be associated with fevers and some fevers result in seizures, one of the things vaccine safety monitoring programs look for is whether vaccines are associated with febrile seizures (seizures caused by a fever). During the past year, there was enhanced focus on monitoring for febrile seizures after influenza (flu) vaccine because in Australia, during the 2010 Southern Hemisphere influenza season, one Australian influenza vaccine was found to increase the chance of febrile seizures in young children who received it. Because of this finding in Australia, one brand of vaccine made by the same manufacturer is not recommended for children under 9 years of age in the United States. After monitoring for febrile seizures during the 2010-2011 influenza season, CDC, FDA, and the Advisory Committee on Immunization Practices (ACIP), reviewed vaccine safety data on febrile seizures in the United States following 2010-11 inactivated influenza and pneumococcal conjugate (PCV 13) vaccines. After thoroughly evaluating the available information, CDC has determined that no changes in the childhood immunization schedule are necessary at this time.

CDC studied the healthcare visit records of more than 200,000 vaccinated children 6 months through 4 years of age through its Vaccine Safety Datalink project during the entire 2010-2011
INACTIVATED INFLUENZA VACCINE
WHAT YOU NEED TO KNOW

2011-12

1 Why get vaccinated?
Influenza (“flu”) is a contagious disease.
It is caused by the influenza virus, which can be spread by
coughing, sneezing, or nasal secretions.
Anyone can get influenza, but rates of infection are highest
among children. For most people, symptoms last only a
few days. They include:
- fever/chills
- sore throat
- muscle aches
- fatigue
- cough
- headache
- runny or stuffy nose
Other illnesses can have the same symptoms and are often
mistaken for influenza.
Young children, people 65 and older, pregnant women, and
people with certain health conditions—such as heart, lung
or kidney disease, or a weakened immune system—can get
much sicker. Flu can cause high fever and pneumonia, and
make existing medical conditions worse. It can cause diabetes
and seizures in children. Each year thousands of people die
from influenza and even more require hospitalization.
By getting flu vaccine you can protect yourself from
influenza and may also avoid spreading influenza to others.

2 Inactivated influenza vaccine
There are two types of influenza vaccine:
1. Inactivated (killed) vaccine, the “flu shot,” is given by
injection with a needle.
2. Live, attenuated (weakened) influenza vaccine is
sprayed into the nose. This vaccine is described in a
separate Vaccine Information Statement.
A “high-dose” inactivated influenza vaccine is available
for people 65 years of age and older. Ask your doctor for
more information.
Influenza viruses are always changing, so annual
vaccination is recommended. Each year scientists try to
match the viruses in the vaccine to those most likely to
cause flu that year. Flu vaccine will not prevent disease
from other viruses, including flu virus not contained in
the vaccine.
It takes up to 2 weeks for protection to develop after the
shot. Protection lasts about a year.

Some inactivated influenza vaccine contains a preservative
called thimerosal. Thimerosal-free influenza vaccine is
available. Ask your doctor for more information.

3 Who should get inactivated influenza vaccine and when?
WHO
All people 6 months of age and older should get flu
vaccine.
Vaccination is especially important for people at higher
risk of severe influenza and their close contacts,
including healthcare personnel and close contacts of
children younger than 6 months.
WHEN
Get the vaccine as soon as it is available. This should
provide protection if the flu season comes early. You can
get the vaccine as long as illness is occurring in your
community.
Influenza can occur at any time, but most influenza occurs
from October through May. In recent seasons, most
infections have occurred in January and February. Getting
vaccinated in December or even later, will still be
beneficial in most years.
Adults and older children need one dose of influenza
vaccine each year. But some children younger than 9 years
of age need two doses to be protected. Ask your doctor.
Influenza vaccine may be given at the same time as other
vaccines, including pneumococcal vaccine.

4 Some people should not get inactivated influenza vaccine or
should wait
- Tell your doctor if you have any severe (life-threatening)
alergies, including a severe allergy to eggs. A severe
allergy to any vaccine component may be a reason not to
get the vaccine. Allergic reactions to influenza vaccine
are rare.
- Tell your doctor if you ever had a severe reaction after a
dose of influenza vaccine.
- Tell your doctor if you ever had Guillain-Barré

www.cdc.gov/vaccines/pubs/vis/
5 What are the risks from inactivated influenza vaccine?

A vaccine, like any medicine, could possibly cause serious problems, such as severe allergic reactions. The risk of a vaccine causing serious harm, or death, is extremely small.

Serious problems from inactivated influenza vaccine are very rare. The viruses in inactivated influenza vaccine have been killed, so you cannot get influenza from the vaccine.

Mild problems:
- soreness, redness, or swelling where the shot was given
- hoarseness: sore, red or itchy eyes; cough
- fever, aches, headache, itching, fatigue

If these problems occur, they usually begin soon after the shot and last 1-2 days.

Moderate problems:
Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time appear to be at increased risk for seizures caused by fever. Ask your doctor for more information.

Tell your doctor if a child who is getting flu vaccine has ever had a seizure.
Proposed Framework for Determining When Vaccine-Associated Febrile Seizures Should Lead to a Change in ACIP Recommendations

• Confirmation of febrile seizures through review of clinical data and standardized classification
• Level of certainty vaccine is causing observed increase in seizures
  – Timing of seizures related to vaccine administration
  – Association with administration of a single vaccine, multiple vaccines, or specific vaccine doses in a series
  – Additional factors that might influence or confound the association (E.g., increased circulation of naturally-occurring infection; medications; underlying conditions)
• Age stratified rate and relative risk of vaccine-associated febrile seizures and excess cases expected in the population
• Evidence for potential explanations (I.e., new product, new vaccine ingredient or manufacturing process, adulterant, etc.)
Proposed Framework for Determining When Vaccine-Associated Febrile Seizures Should Lead to a Change in ACIP Recommendations

- Benefits of vaccine(s) associated with seizures by age group (key outcomes prevented)
- Effect of vaccine(s) on preventing febrile seizures
- Association expected to be temporary or ongoing?
- Potential for change in recommendations to result in missed opportunities to vaccinate or unintended decreased vaccine uptake with resulting increase in naturally-occurring infections
- Acceptability to healthcare providers and the public of potential options under consideration for change in recommendations
- Programmatic implications and feasibility of making changes in recommendations
"If it were painful, could I do this?"