Safety of the Trivalent Inactivated Influenza Vaccine (TIV) Among Children: A Population-Based Study

Vaccine Safety Datalink (VSD)
Kaiser Permanente Colorado
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Contributors

• Eric France, MD, MSPH, KP Colorado
• Jason Glanz, MS, KP Colorado
• Simon Hambidge, MD, Denver Health
• Stanley Xu, PhD, KP Colorado
• Bob Davis, MD, MPH, University of WA
• Bill Barlow, PhD, University of WA
• VSD Investigator Team
Hypothesis Generating Studies

- VAERS: Signal Detection
- Post-Marketing Studies: Required by FDA with new vaccine (N: 50,000 - 100,000)
- VSD Database Screening Study
Flu Vaccine Safety Studies

• Confounding by Indication:

Asthmatics who are vaccinated are more likely to wheeze than asthmatics who are not vaccinated

Self-Control methods adjust for important unknown confounders, including severity of illness
Flu Vaccine Safety Studies

- **Issue of Seasonality:**
  - Flu Vaccine administered in a defined period (October - February)
  - Exposure and Control periods may differ in important ways because of seasonal differences

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Flu Shot, Oct 1

Dec 1
# Safety of Pediatric TIV Vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>TIV N</th>
<th>Safety Data?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piedra, 1991</td>
<td>191</td>
<td>No</td>
</tr>
<tr>
<td>Heikkinen, 1991</td>
<td>187</td>
<td>No</td>
</tr>
<tr>
<td>Clements, 1995</td>
<td>93</td>
<td>No</td>
</tr>
<tr>
<td>Piedra, 1993</td>
<td>12</td>
<td>Yes</td>
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<tr>
<td>Gonzalez, 2000</td>
<td>67</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuzil, 2001</td>
<td>791</td>
<td>Yes</td>
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</table>
Objective

To screen a large cohort of children who received the TIV for evidence of medically attended events (MAE) following vaccination
VSD Databases

- > 3,500,000 children under 18 years of age
- 5 MCOs: KP Northern California, KP Southern California, GHC, KP Northwest, and KP Colorado
- Data ranging 1/1/93 - 12/31/99
- 251,600 children who received 438,167 TIV vaccinations
Risk and Control Periods:

Risk Period:
Days 1-14

Control Group 1:
Days -28 -14

Flu Vaccination
Day 0

Control Group 2:
Days 15 - 28
Interpretations of Odds Ratios

Given that an individual experienced an MAE, what are the odds that the MAE occurred in the post-vaccination risk period compared to a control period?
VSD TIV Dataset:

- Five sites: GHC, KP Northwest, KP Northern California, KP Southern California, KP Colorado
- Outpatient/ED visits, 1/1/95 - 12/31/99
- Inpatient visits, 1/1/93 - 12/31/99
- Children who received at least one TIV shot
- First shot if child received two in a season
• 251,600 individuals who received 438,167 shots

• 1,165 diagnosis codes occurred during the 2 weeks following flu vaccination
Examples of Roll-up Variables

- Otitis media
- URI/Cold
- Pharyngitis
- Urticaria
- Limb soreness
- Rash
- Allergic Reaction
Outpatient

221,484 Shots

Sample 1
110,742 Shots

Sample 2
110,742 Shots

P < .05 compared to EITHER control group

Remove codes not biologically plausible

Confirm against Sample 2
Final Steps

- ORs > 1 and p < .05 in both samples
  - Medical chart review on the cases to confirm case status
  - Reanalyze data with confirmed incident cases
Sample 1
1,165 Dx Codes

P < .05 compared to EITHER control group

43 Dx Codes

Sample 2
33 Dx Codes

33 Dx codes pushed against SAMPLE 2

Drop 10 Dx Codes not biologically plausible

11 Diagnosis Codes, P < .05
Dx Codes Not Plausible

- Tuberculin Test Reaction (7955)
- Infestation NOS (1349)
- Insect Bite (9194, 9195)
- Obesity (2780)
- Sprain of Neck (8740)
- Sprain of Shoulder (8409)
- Sprain of Elbow (8419)
- Sprain of Lumbar Region (8472)
- Dislocated Knee (8140)
Analyses

• Settings: outpatient, inpatient and ED

• Risk windows
  – 14-day risk window
  – 3-day risk window
  – 0 - 2-day risk window
Analyses

• 6 - 23 month age group: all three medical settings and three risk windows

• OR ≥ 2.5 and p ≤ 0.20
Statistical Power

• Need 68 cases to detect an OR = 2 with 0.80 power and $\alpha = 0.05$

• Case numbers for common symptoms reported following vaccination
  
  – Fever: 110 cases
  – Convulsions: 82 cases
  – Dyspnea: 512 cases
<table>
<thead>
<tr>
<th>Description</th>
<th>OR11</th>
<th>OR12</th>
<th>OR21</th>
<th>OR22</th>
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</thead>
<tbody>
<tr>
<td>Diabetes Uncomplicated</td>
<td>1.29</td>
<td>NS</td>
<td>1.41</td>
<td>NS</td>
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<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URI/Cold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0.65</td>
<td>—</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Chronic Rhinitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis Media</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Diabetes, Uncomplicated

• ICD 9 Code 2500

• 87% of visits on chart audit were for health maintenance (well visit)

• More likely to receive routine diabetes care in 2 weeks following flu shot than in control

• OR = 0.76 (95% CI 0.4 - 1.4)
Why negative Odds Ratios?

- “Healthy Vaccinee” Effect
- “Vaccinated When Sick” Effect
Risk and Control Periods:

Risk Period:
Days 1-14

Control Group 1:
Days -28 -14

Flu Vaccination
Day 0

Control Group 2:
Days 15 - 28
Why negative Odds Ratios?

• “Healthy Vaccinee” Effect

• “Vaccinated When Sick” Effect
6 – 23 months

8476 shots

Control 1

Control 2
<table>
<thead>
<tr>
<th>Description</th>
<th>OR1</th>
<th>OR2</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic Dermatitis</td>
<td>1.94</td>
<td>NS</td>
<td>1.05 – 3.39</td>
</tr>
</tbody>
</table>

URI/Cold
Asthma
Chronic Rhinitis
Dyspnea/Respiratory ABN

0.42 — 0.84

*Complete sample used, 8476 shots; P < 0.05
Chart Review: Atopic Dermatitis

- 52 verified visits
- 60% were not a new case
- 24% clearly a new case; 16% could not tell
- OR: 2.2 (95% CI 0.8 - 5.7)
<table>
<thead>
<tr>
<th>Description</th>
<th>OR1</th>
<th>OR2</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impetigo</td>
<td>NS</td>
<td>8.00</td>
<td>1.01 – 62.5</td>
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</tbody>
</table>

URI/Cold, Asthma, Rhinitis, Dyspnea, Pharyngitis

*Complete sample used, 8476 shots; P < 0.05*
<table>
<thead>
<tr>
<th>Description</th>
<th>OR11</th>
<th>OR12</th>
<th>OR21</th>
<th>OR22</th>
<th>Combined Sample</th>
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</thead>
<tbody>
<tr>
<td>Renal and Ureteral Disorder</td>
<td>-</td>
<td>3.50</td>
<td>-</td>
<td>5.00</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.13 –14.17)</td>
</tr>
</tbody>
</table>
Renal and Ureteral Disorder, NOS

- 25 of the 26 cases were pre-existing disorders
- 20 of 26 visits were for a renal/ureteral dx
- Wide variation in diagnoses
- OR 2.0 (95% CI 0.6 - 6.6)
Conclusions

- No signal of a serious medical outcome occurring more often in the two weeks following flu vaccination
- No neurologic outcomes identified
- Impetigo signal identified
Neurologic Disorders

- 11 Roll-up Variables created (e.g., Meningoencephalitides; Movement Disorders), many with small numbers

- Split sample design; 2 week exposure window; 2 control periods

- Movement Disorder OR = 2.8 (P < .05)
Movement Disorder

- Split Sample collapsed; Movement Disorder not significant against either control group

- Ataxia (ICD: 781.3) noted among cases

- Ataxia OR 7.0 (P < .05) 95% CI 1.6 - 31
  - 14 cases in risk window; 2 cases in post vax control window
Ataxia (ICD-9 781.3)

- Of 16 cases, 8 occurred at KP Colorado
- 6 of 8 occurred in a two week period
- Chart audit of 5 charts: all with dx of ADHD, seen by specific M.D. None with acute ataxia.
Conclusions

• New analyses of roll-up neurologic outcomes identified a signal for ataxia that was due to a coding error at KPC.

• Phase II Pediatric safety study to begin this summer, focused on 6-23 month children, with up to 6 weeks follow-up