

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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# 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



# Safety of Pediatric TIV Vaccine

<i>Study</i>	<i>TIV N</i>	<i>Safety Data?</i>
Piedra, 1991	191	No
Heikkinen, 1991	187	No
Clements, 1995	93	No
Piedra, 1993	12	Yes
Gonzalez, 2000	67	Yes
Neuzil, 2001	791	Yes

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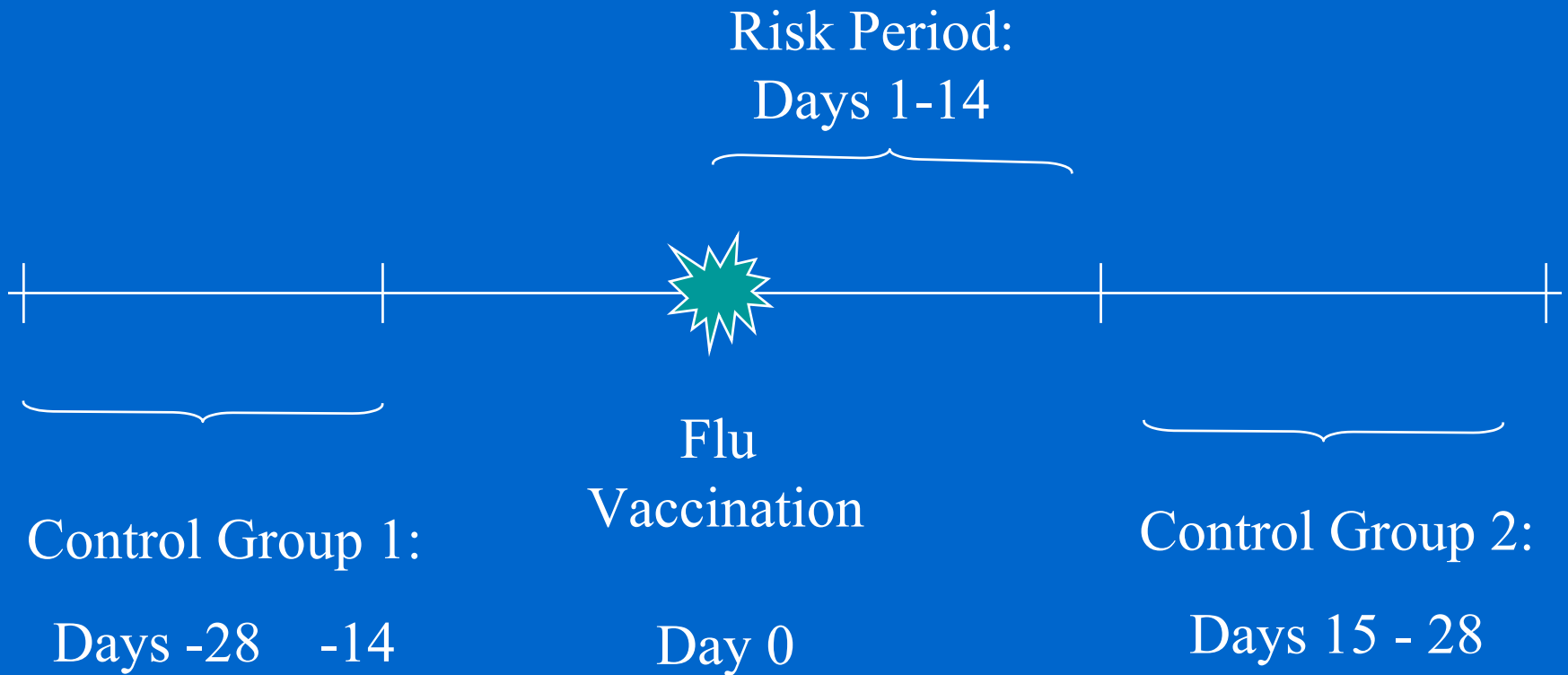
# Objective

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:



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## 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

## VSD TIV Data Set (cont'd)

- 251,600 individuals who received 438,167 shots
- 1,165 diagnosis codes occurred during the 2 weeks following flu vaccination

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# Examples of Roll-up Variables

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

# Outpatient



$P < .05$  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



11 Diagnosis Codes,  $P < .05$



Sample 2  
33 Dx Codes

33 Dx codes pushed  
against SAMPLE 2



Drop 10 Dx Codes not  
biologically plausible

# 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
- $OR \geq 2.5$  and  $p \leq 0.20$

# 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

# Outpatient 1-14 Days

<i>Description</i>	<i>OR11</i>	<i>OR12</i>	<i>OR21</i>	<i>OR22</i>
<b>Diabetes Uncomplicated</b>	<b>1.29</b>	<b>NS</b>	<b>1.41</b>	<b>NS</b>

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Sinusitis

URI/Cold

Asthma

Chronic Rhinitis

Otitis Media

0.65 — 0.88

# Diabetes, Uncomplicated

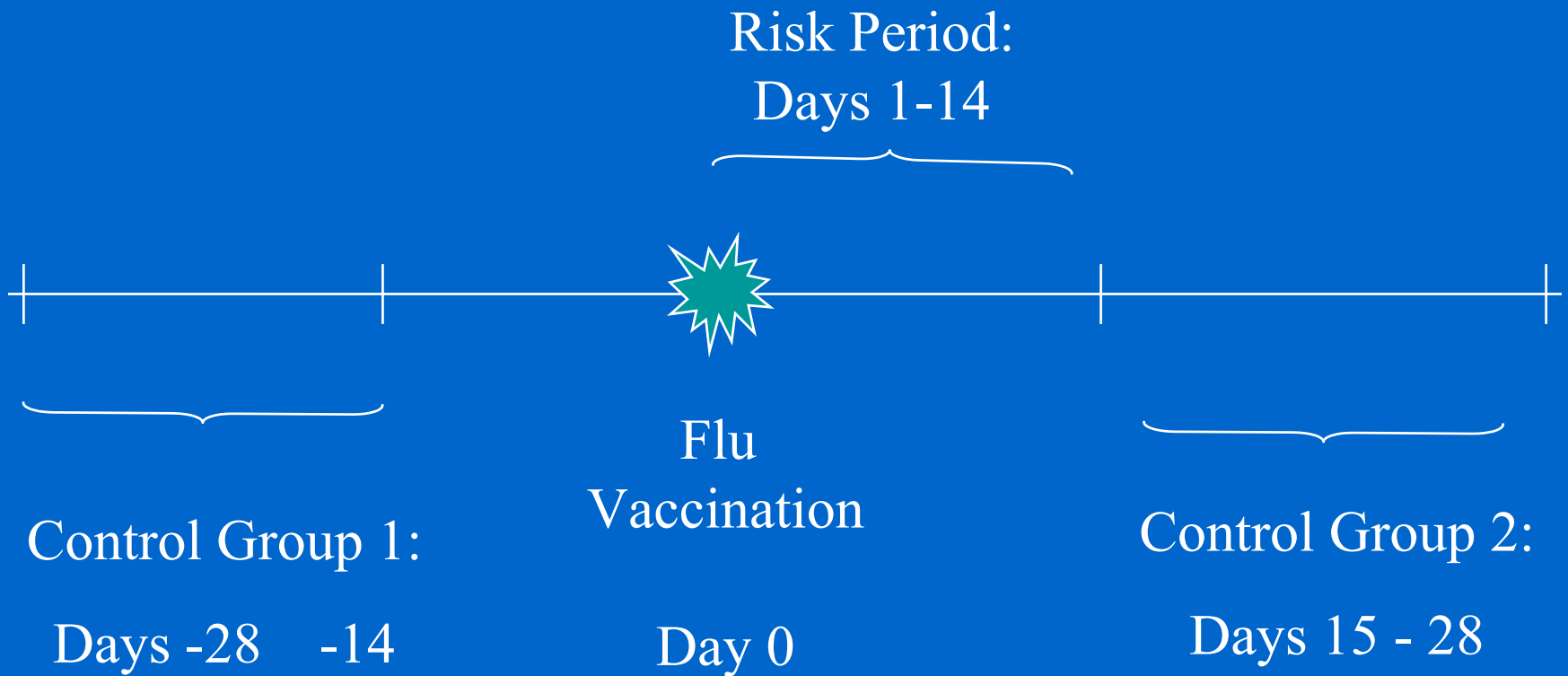
- ICD 9 Code 2500
- 87% of visits on chart audit were for health maintenance (well visit)
- More likely to receive routine diabetes care in 2 weeks following flu shot than in control
- OR = 0.76 (95% CI 0.4 - 1.4)

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# Why negative Odds Ratios?

- “Healthy Vaccinee” Effect
- “Vaccinated When Sick” Effect

# Risk and Control Periods:



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# Why negative Odds Ratios?

- “Healthy Vaccinee” Effect
- “Vaccinated When Sick” Effect

**6 – 23 months**



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# Outpatient 1-14 Days, 6 – 23 months\*

<i>Description</i>	<i>OR1</i>	<i>OR2</i>	<i>95% CI</i>
<b>Atopic Dermatitis</b>	<b>1.94</b>	<b>NS</b>	<b>1.05 – 3.39</b>

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URI/Cold

Asthma

Chronic Rhinitis

Dyspnea/Respiratory  
ABN

0.42 — 0.84

\*Complete sample used, 8476 shots; P < 0.05

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# 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)

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# Outpatient 1-3 Days, 6 – 23 months\*

<i>Description</i>	<i>OR1</i>	<i>OR2</i>	<i>95% CI</i>
<b>Impetigo</b>	<b>NS</b>	<b>8.00</b>	<b>1.01 – 62.5</b>

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URI/Cold

Asthma

Rhinitis

Dyspnea

Pharyngitis

0.13 — 0.50

\*Complete sample used, 8476 shots; P < 0.05

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Outpatient 1-14 Days,  $OR \geq 2.5$  and  $P \leq 0.20$

<i>Description</i>	<i>OR11</i>	<i>OR12</i>	<i>OR21</i>	<i>OR22</i>	<i>Combined Sample</i>
Renal and Ureteral Disorder	-	3.50	-	5.00	3.99 (1.13 –14.17)

# 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., Meningoencephalitis; 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