# Assessment of febrile seizures after trivalent influenza vaccines during the 2010-2011 influenza season in PRISM

Alison Tse Kawai, ScD
Harvard Medical School
On Behalf of the Mini-Sentinel PRISM Team

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# Background

- Vaccine Safety Datalink (Tse et al., 2011)
  - 2010-11 TIV and PCV13 each associated with increased risk of febrile seizures (FS)

| | IRR (95% CI) |
|---|---|
| TIV | 2.4 (1.2, 4.7) |
| PCV13 | 2.5 (1.3, 4.7) |

  - Risk difference calculations suggested a greater risk of FS with same day TIV and PCV13 vaccination
  - Preliminary findings reported to ACIP in Feb. 2011
  - Vaccine Information Statement updated to include statement on increased risk w/ same day TIV + PCV13

# Background

- Vaccine Adverse Events Reporting (Leroy et al., 2011)
  - Disproportional reporting of FS following 2010-11 FluZone
  - FDA notice of VAERS findings on website in Jan. 2011

# Study Questions

Among children 6-59 months of age in the 2010-11 influenza season

(1) Was exposure to TIV or PCV13 associated with a greater risk for FS when compared to unexposed periods?

(2) Assuming children received both TIV and PCV13, did administering them on the same day lead to a greater risk for FS when compared to separate days?

# Study Population

- **P**ost-licensure **R**apid **I**mmunization **S**afety **M**onitoring system

- Component of the FDA-sponsored Mini-Sentinel Pilot Program developed to conduct active surveillance for medical product safety

- PRISM Data Partners currently include five health insurance companies

# Study Population and Design

- Study population
  - Three PRISM Data Partners participating at time of study: Aetna, Health Core, Humana
  - Children 6-59 months of age vaccinated between July 1, 2010 to June 30, 2011

- Self-controlled risk interval design

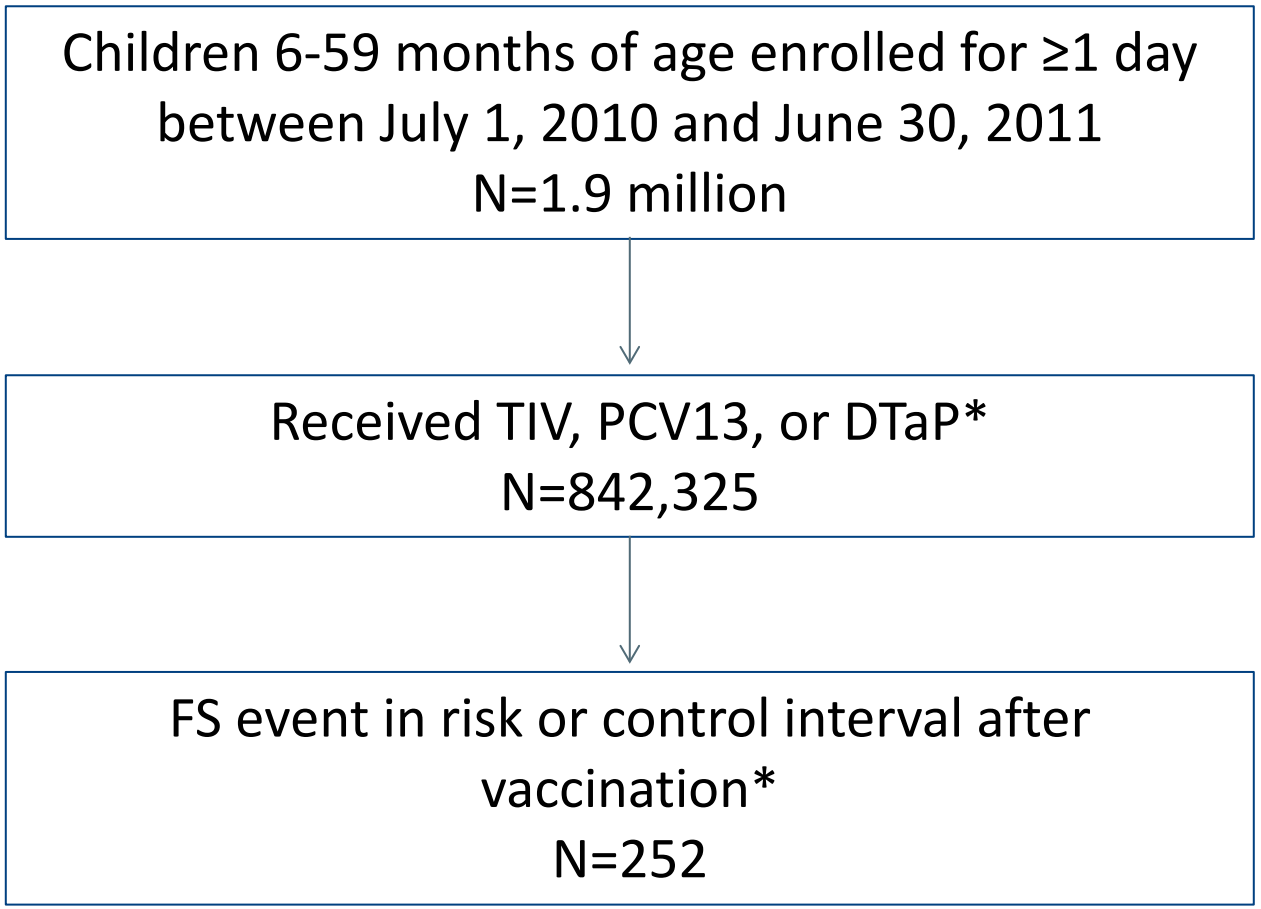
# Exposures

- Exposures to TIV, PCV13, and DTaP or DTaP combination vaccines identified in claims and immunization registry data
- Validated TIV, PCV13, and DTaP in medical records if available
- Excluded cases later confirmed as LAIV or PCV7 exposed

# Outcomes

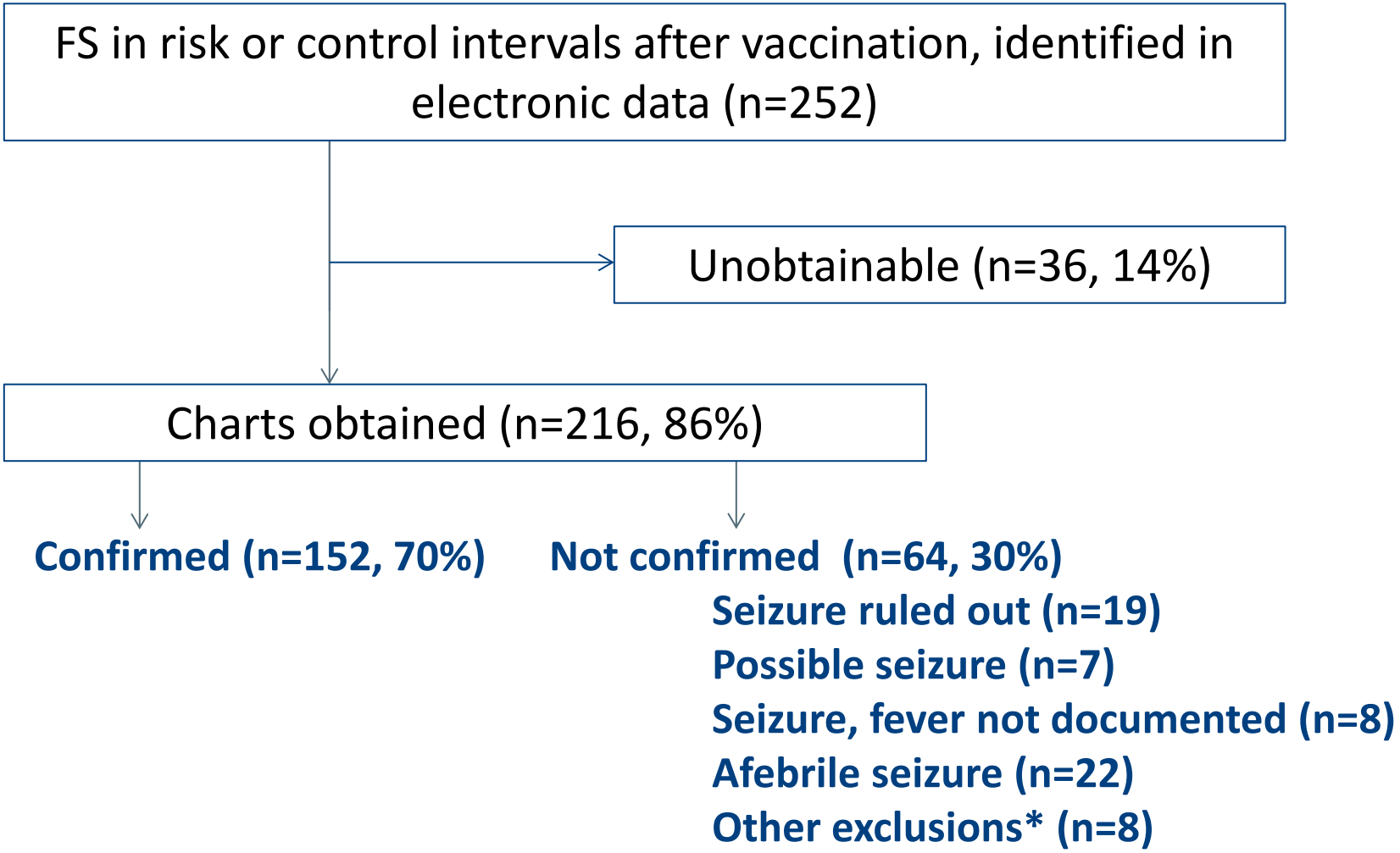
- Outcomes identified in claims data
  - ICD9 codes 780.3, 780.31, 780.32, or 780.39
  - Inpatient and ED settings only
- Validated FS status with medical record review
- Clinician adjudicators confirmed FS
  - Seizure and fever within 24 hours or dx of FS
  - Excluded those w/ conditions in AAP treatment guidelines
  - Excluded focal seizures unless complex FS

# Study Population




*According to claims and immunization registry data

# Febrile Seizure Confirmation Status




*Seizure associated with metabolic disorder, CNS inflammation/infection, hx of afebrile seizures, or focal seizure not associated with complex febrile seizure

# Vaccine Confirmation Status

- Medical records were available for majority of vaccinations identified in claims or registry data
  - 79% charts available for TIV exposure
  - 91% charts available for PCV13 exposure
  - 91% charts available for DTaP exposure

- Vaccine confirmation rates were high when charts available
  - TIV or influenza vaccine chart confirmed in 98% of cases
  - PCV13 or PCV chart confirmed in 94% of cases
  - DTaP chart confirmed in 100% of cases

- Analysis included vaccines identified in electronic data or in medical records

- Among confirmed FS cases, 5 were excluded because medical records indicated that seizures occurred outside of risk or control interval and 5 were excluded because LAIV or PCV7 was identified in the medical record

| Characteristic | No. Confirmed Cases N=142 |
|---|---|
| **Age at vaccination** | |
| 6-11 months | 18 (13%) |
| 12-15 months | 50 (35%) |
| 16-23 months | 38 (27%) |
| 24-35 months | 27 (19%) |
| 36-47 months | 3 (2%) |
| 48-59 months | 6 (4%) |
| **Setting of diagnosis** | |
| ED | 130 (92%) |
| Inpatient | 12 (8%) |

| Characteristic | No. Confirmed Cases N=142 |
|---|---|
| **Vaccinations*** | |
| TIV + PCV13 + DTaP | 8 (6%) |
| TIV + PCV13 | 8 (6%) |
| TIV + DTaP | 12 (8%) |
| PCV13 + DTaP | 20 (14%) |
| TIV | 40 (28%) |
| PCV13 | 35 (25%) |
| DTaP | 19 (13%) |

*All +/- other vaccines

(1) In the 2010-11 influenza season, was exposure to TIV or PCV13 associated with a greater risk for FS, when compared to unexposed periods?

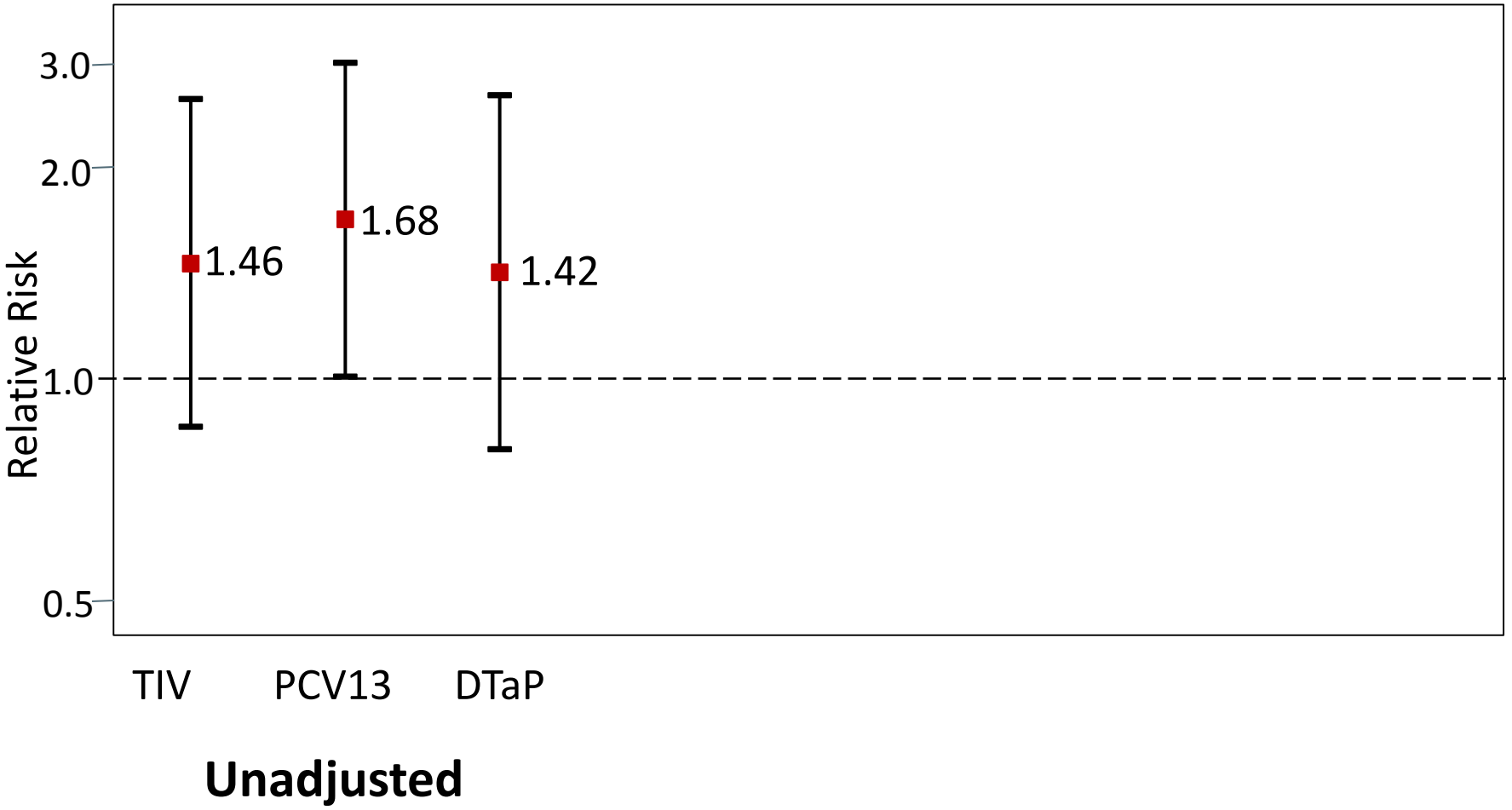
*Relative risk and attributable risk estimates*

# Relative Risk Estimates

- Conditional Poisson modeling
  1. Unadjusted
  2. Adjusted for age and calendar time
  3. Primary analysis: Adjusted for age, calendar time, and vaccines of interest

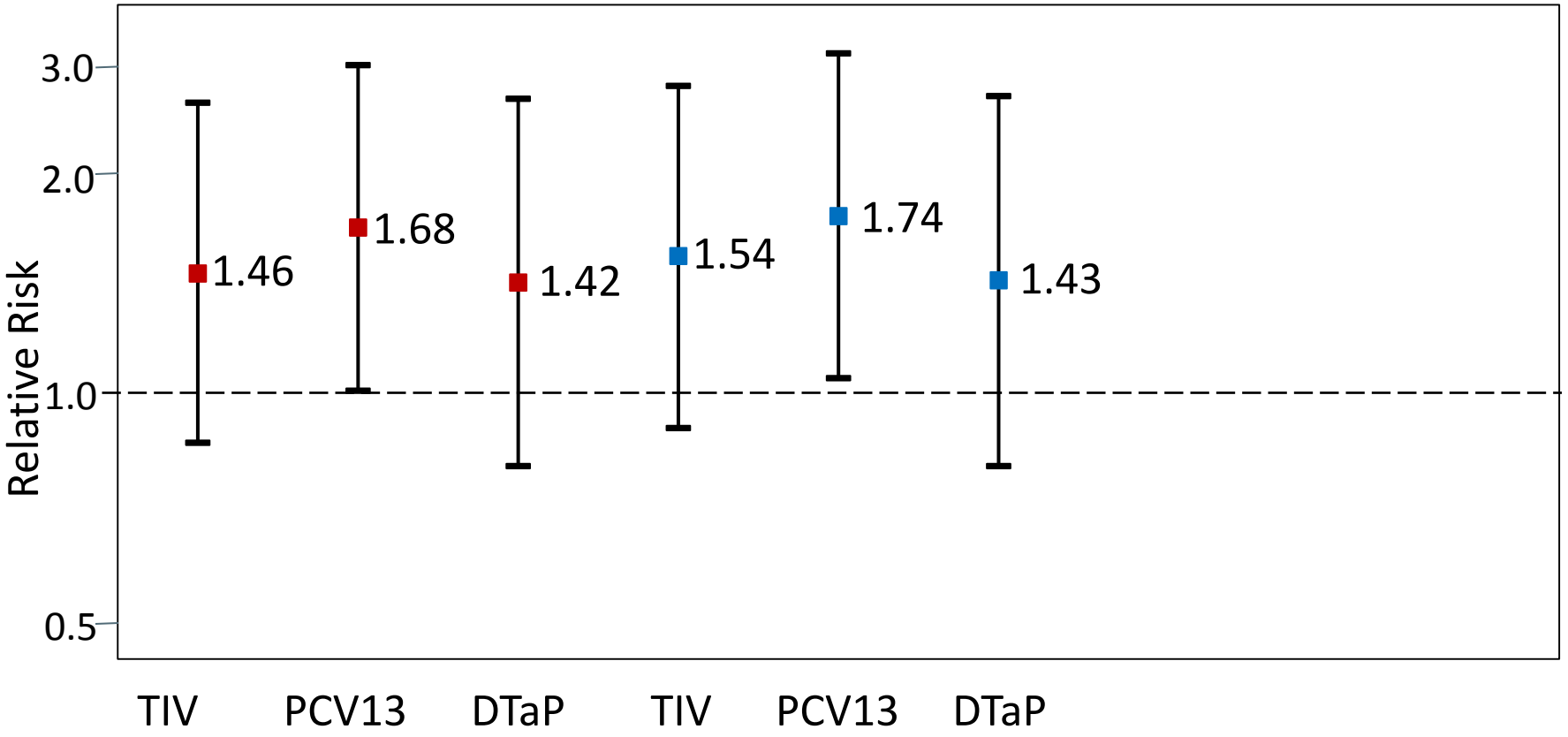
- Age and calendar time adjustments
  - Included person time from underlying PRISM cohort
  - Quadratic splines used to adjust for age and calendar time

# Relative Risk Estimates

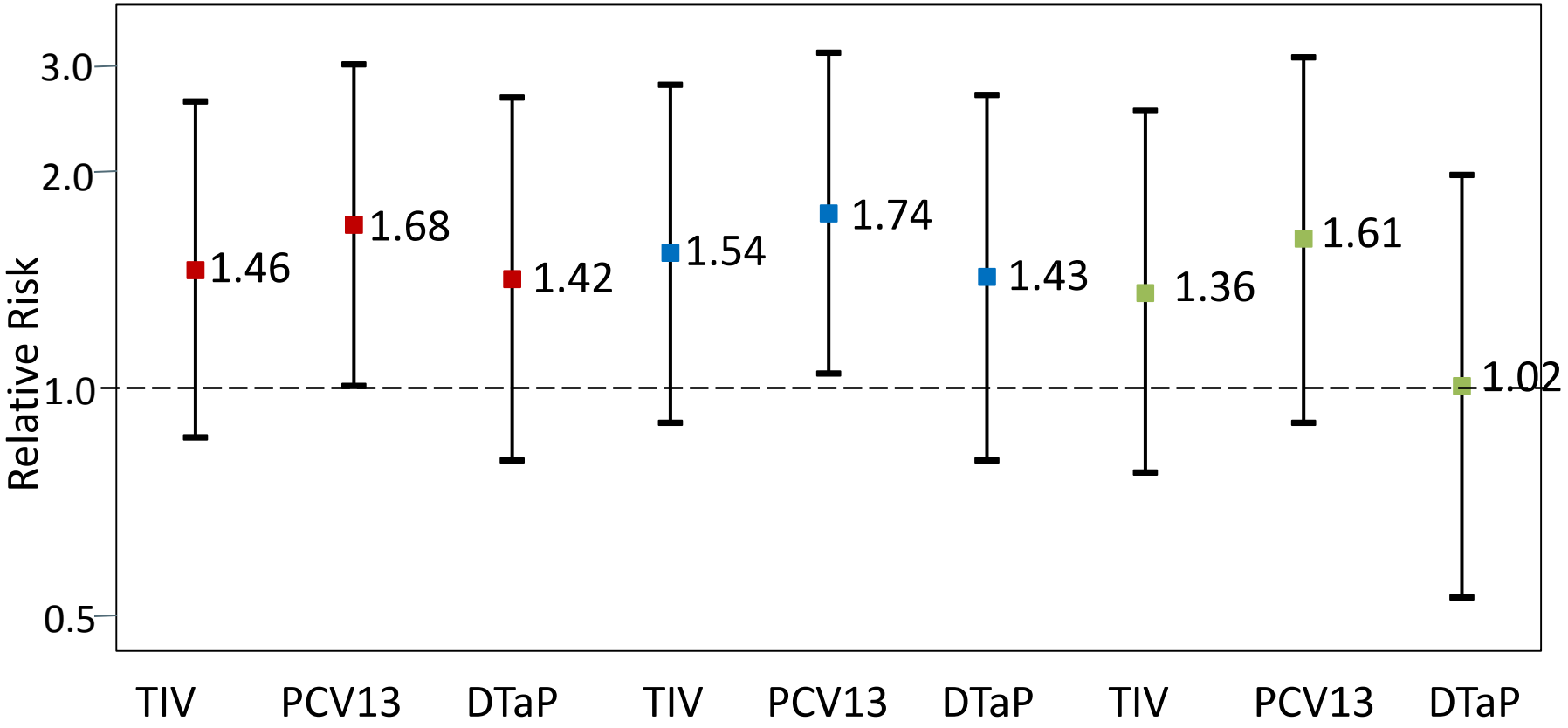



**Unadjusted**

# Relative Risk Estimates



# Relative Risk Estimates




**Unadjusted**

**Age & calendar time adjusted**

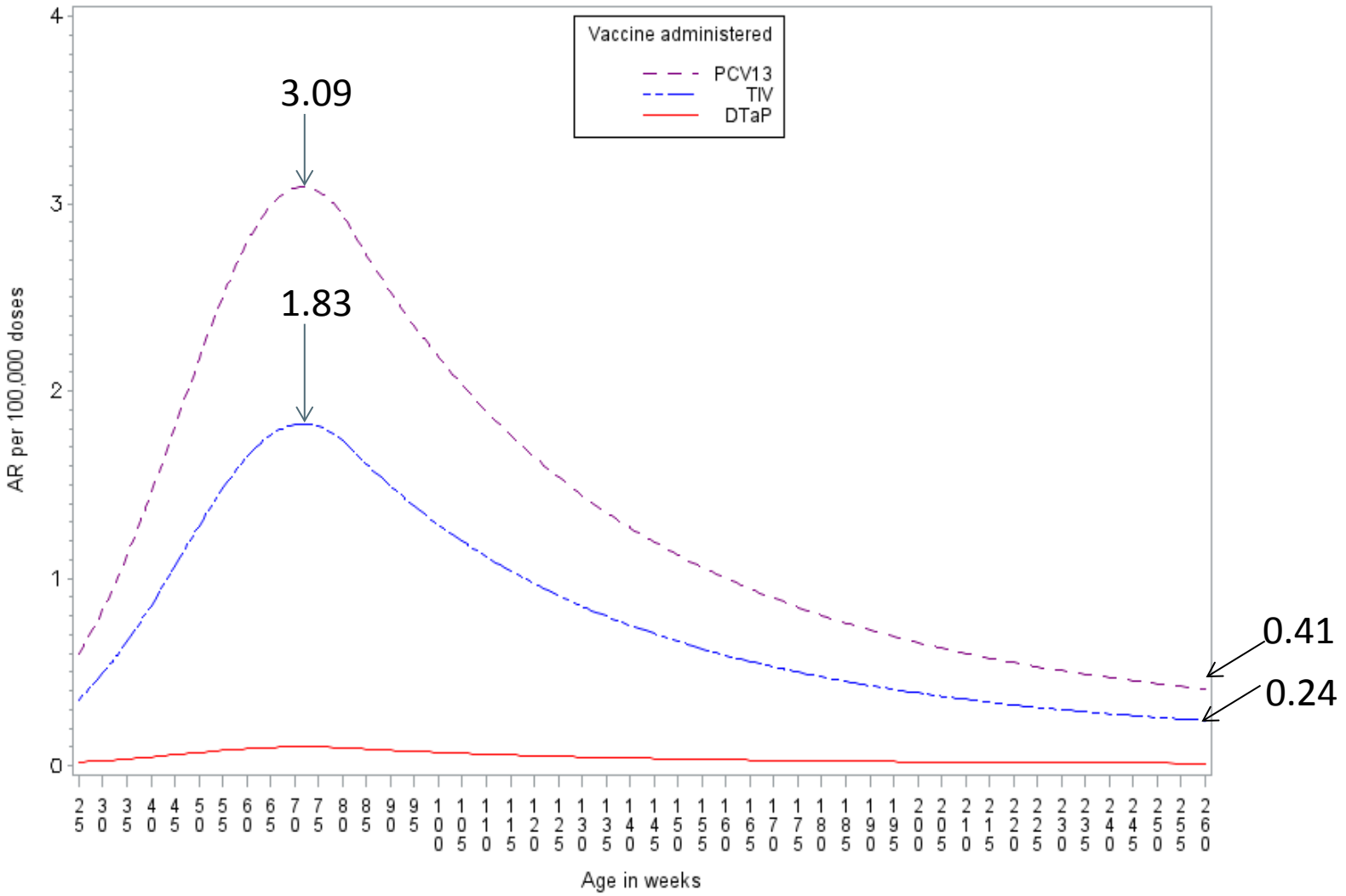
**Primary analysis: Age, calendar time, & vaccine adjusted**

# Attributable Risk Estimates

- Attributable risk estimated by age in weeks
- AR= (IRR-1)*$p_0$*PPV*2
  - IRR= Incidence rate ratios from primary model
  - $p_0$= Baseline rate of claims-identified seizures in PRISM population
  - PPV= Positive predictive value of claims codes
  - 2= Length of risk interval in days

- IRR assumed to be constant across age
- Baseline rate based on quadratic spline for age
- PPV based on chart review of control interval cases

# Attributable Risk Estimates



# Attributable Risk Estimates Based on Upper Limit of 95% CI for Relative Risks

| Age | AR per 100,000 doses, based on upper limit of 95% CI for RR* | |
|---|---|---|
| | TIV | PCV13 |
| **260 weeks** (~59 months) | 0.93 | 1.22 |
| **72 weeks** (~16 months) | 7.05 | 9.23 |

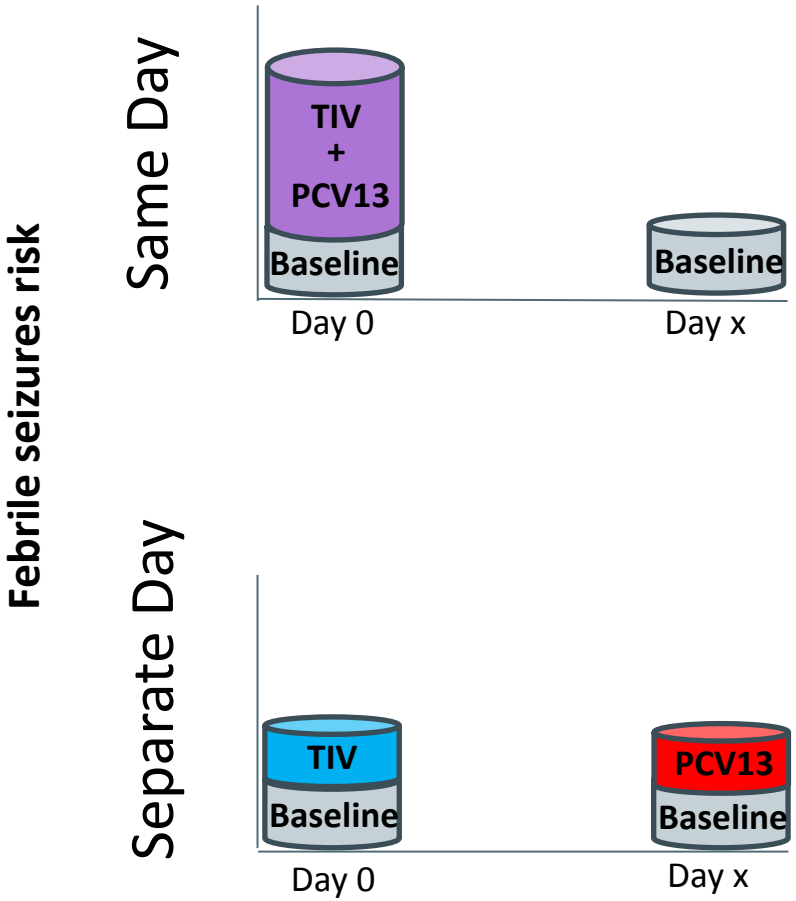
*Baseline risk of FS, 6-59 months of age: 2774.72 per 100,000 children

(2) Assuming children received both TIV & PCV13 in the 2010-11 influenza season, did administering them on the same day lead to a greater risk for FS when compared to separate days?

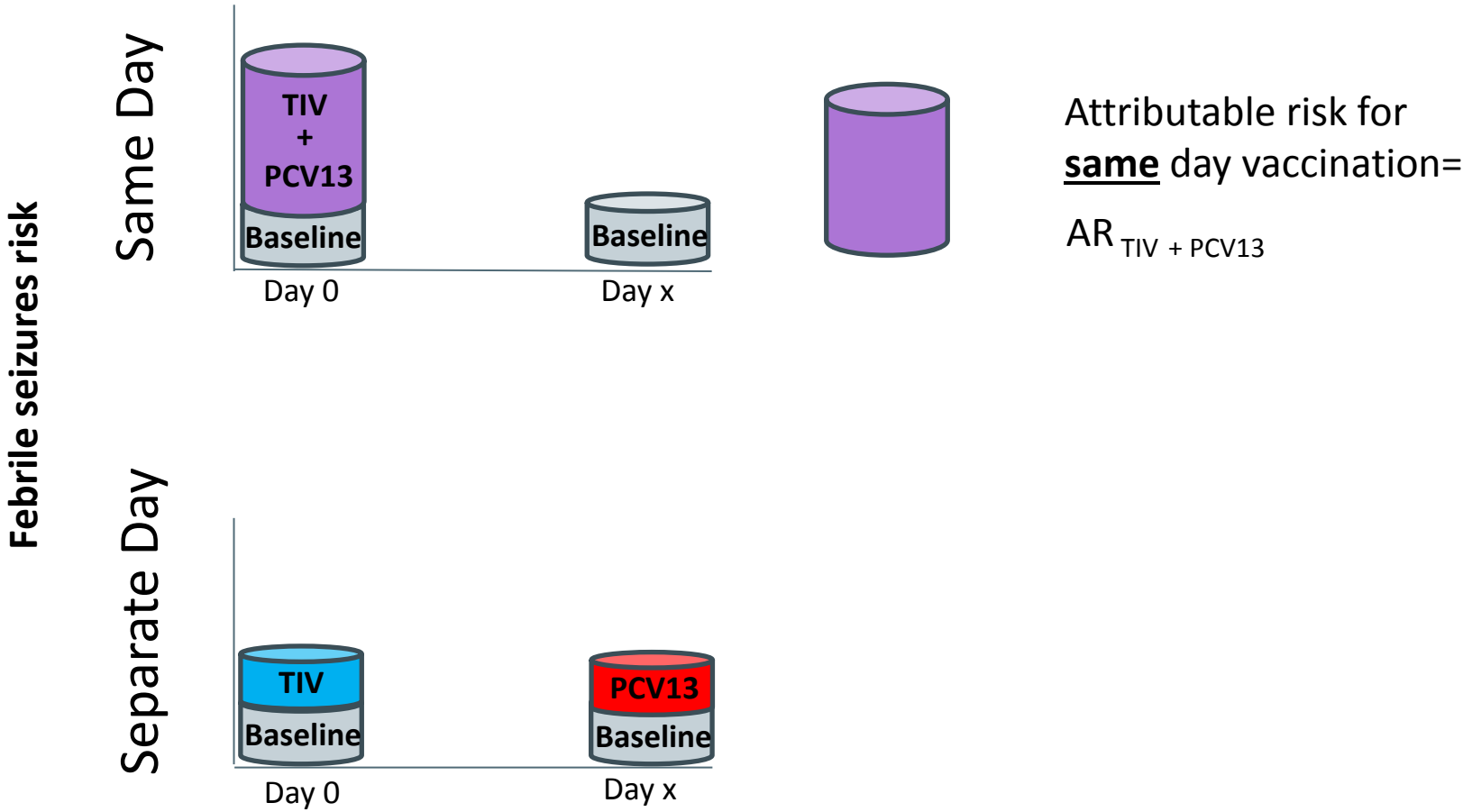
*Difference in attributable risk for same day vaccination vs. that for separate day vaccination**

*ARs translated from IRR estimates based on self-controlled risk interval design

# Same Day vs. Separate Day TIV + PCV13



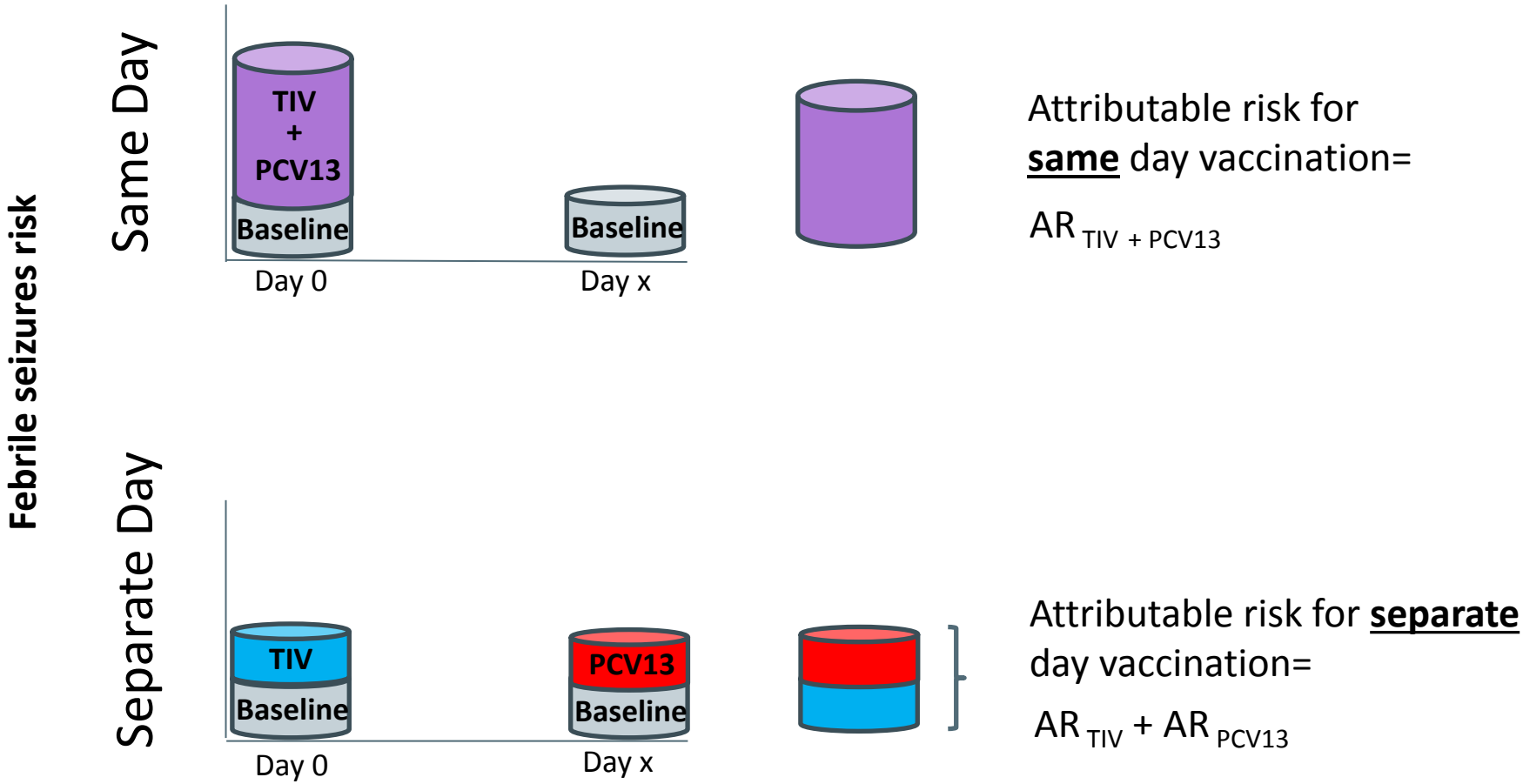
# Same Day vs. Separate Day TIV + PCV13



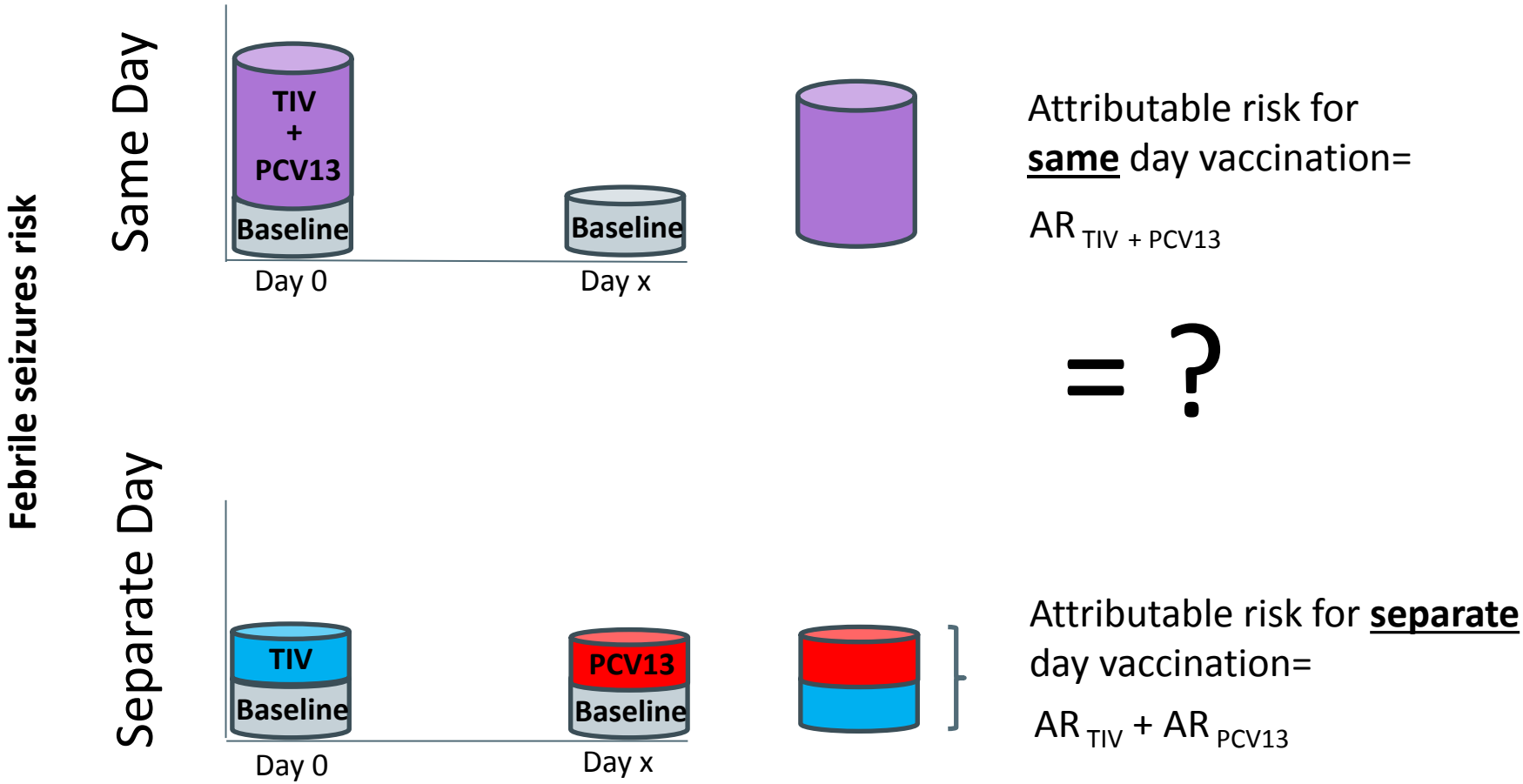

Attributable risk for **same** day vaccination=

$AR_{TIV + PCV13}$

# Same Day vs. Separate Day TIV + PCV13



# Same Day vs. Separate Day TIV + PCV13



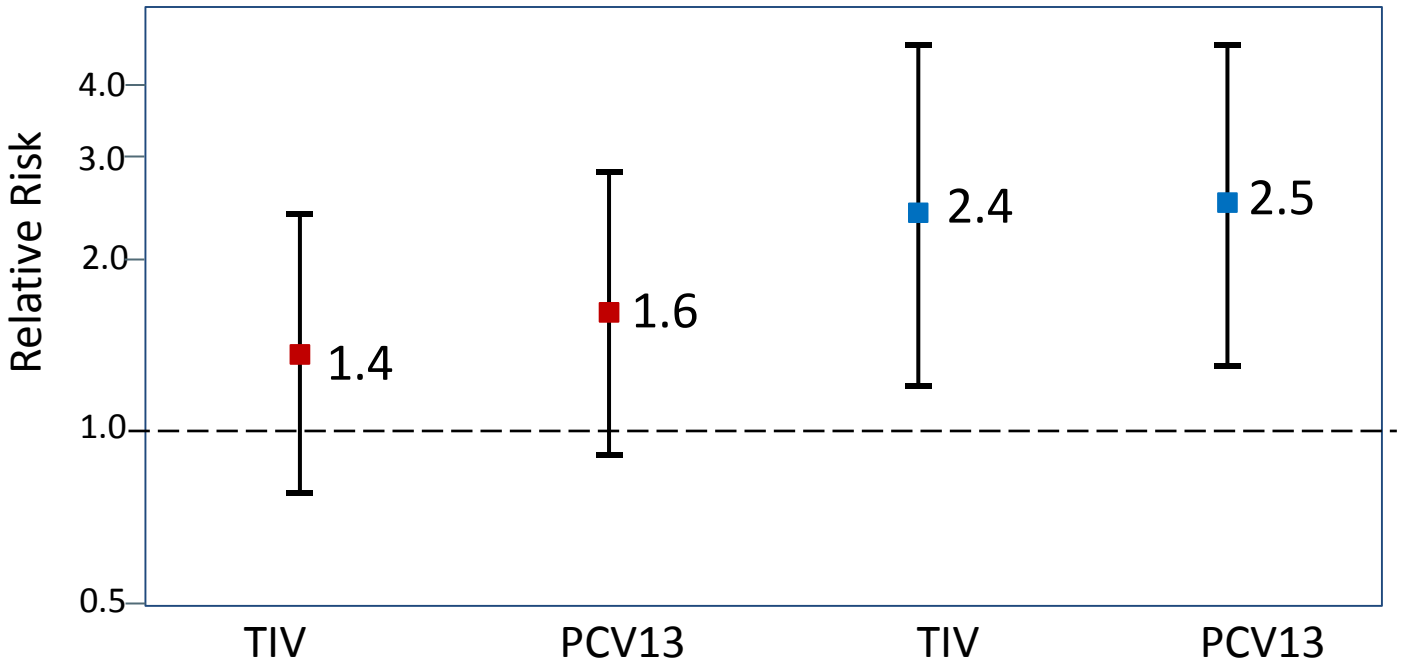
# Same Day Vs. Separate Day TIV + PCV13

- Assuming children received both TIV and PCV13 in the 2010-11 influenza season
  - Same day TIV & PCV13 vaccination was not significantly associated with excess risk of febrile seizure when compared to separate day vaccination

- Difference in excess risk
  - Same day vaccination: 1.08 fewer febrile seizures per 100,000 children (95% CI -5.68 to 6.09 per 100,000 children)

# Discussion

# Comparison of Relative Risk Estimates




| Interval | No. cases | | | |
|---|---|---|---|---|
| Risk interval | 20 | 23 | 25 | 29 |
| Control interval | 48 | 48 | 22 | 27 |
| Total | 68 | 71 | 47 | 56 |

# Comparison of Same Day Vs. Separate Day Vaccination of TIV + PCV13

| Study | Excess risk for same day vaccination (FS per 100,000 children) | 95% CI |
|---|---|---|
| **PRISM (Kawai et al.)** | -1.1 | -5.68 to 6.09 |
| **VSD (Tse et al, 2011)** | 7.3 | Not computed |

# Strengths and Limitations of PRISM study

**Strengths**

- Self-controlled risk interval design
- Rigorous adjudication of febrile seizure cases by 2 pediatricians
- Age, calendar time, and DTaP vaccine adjustments
- 80% power to detect IRRs ~2

**Limitations**

- Inability to validate all vaccine exposures
- Limited power to detect IRRs <2

# Conclusions

- In the 2010-11 season, IRR point estimates for TIV and PCV13 were above 1, but TIV, DTaP, and PCV13 were not significantly associated with FS in the primary analytic models

- If increased risks for TIV and for PCV13 existed
  - Magnitude of IRRs is lower than originally thought
  - ARs based on the upper bound of 95% CI for IRRs would correspond to modest excess risks

- Assuming children received both TIV and PCV13
  - Administering both vaccines on the same day was not significantly associated with risk of FS when compared to separate day vaccination

# Acknowledgments (partial)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Meghan Baker

Carolyn Balsbaugh

David Cole

Claudia Coronel-Moreno

Ashleigh Goff

## MS/PRISM team (cont'd)

Robert Jin

Tricia Kennedy

Martin Kulldorff

Grace Lee

Lingling Li

Linda Pointon

Megan Reidy

Robert Rosofsky

Diana Santiago

Katherine Yih

## Clinical adjudicators

Sangeeth Gnanasekaran

Sarah Henrickson