Brookings Webinar on Active Medical Product Surveillance

Findings from a Mini-Sentinel Medical Product Assessment: Influenza Vaccines and Risk of Febrile Seizures

Engelberg Center for Health Care Reform
The Brookings Institution
July 21, 2014

Introduction to PRISM Febrile Seizures Study

Michael Nguyen, MD
Division of Epidemiology, Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
July 21, 2014

Brookings Institution Webinar

Febrile Seizures

- Defined as seizures accompanied by fever in children aged 6 – 59 months, without evidence of central nervous system infection, metabolic abnormality, or underlying seizure disorder
  - Precise link between fever and seizure not clear
  - Generally benign; rarely associated with neurologic sequelae
  - Small increase in risk of subsequently developing epilepsy

- Occurs in 2-5% of children aged <5 years
  - Associated with febrile illness caused by viral and bacterial infections
  - Risk increased after whole cell pertussis (DTP), measles containing vaccines
  - 35% overall recurrence rate, higher in younger children

Importance of Febrile Seizure after Vaccination

- First associated with an influenza vaccine during the 2010 southern hemisphere season (CSL Fluvax trivalent inactivated vaccine)
  - Unexpected increased risk of <9 cases per 1,000 doses administered*
  - Onset typically within 8 hours post-vaccination

- Resulted in multiple public health interventions worldwide, notably:
  - Suspension of mass vaccination program in Australia for children <5 years
  - Recommendation against use of CSL Afluria in the United States for children aged 6 months through 8 years by Advisory Committee on Immunization Practices (ACIP)
  - Added data to Warnings and Precautions section of CSL Afluria prescribing information and restriction of the indication for use to children ≥5 years**

* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm
** http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm220764.htm

Unique Features of Influenza Vaccine

Rationale for Safety Monitoring

- Widest ACIP recommendation for use among all vaccines
  - Routinely recommended for all persons aged ≥6 months since 2010
  - Annual vaccination, with potential for different formulations each year
  - Often administered with a wide range of other vaccines

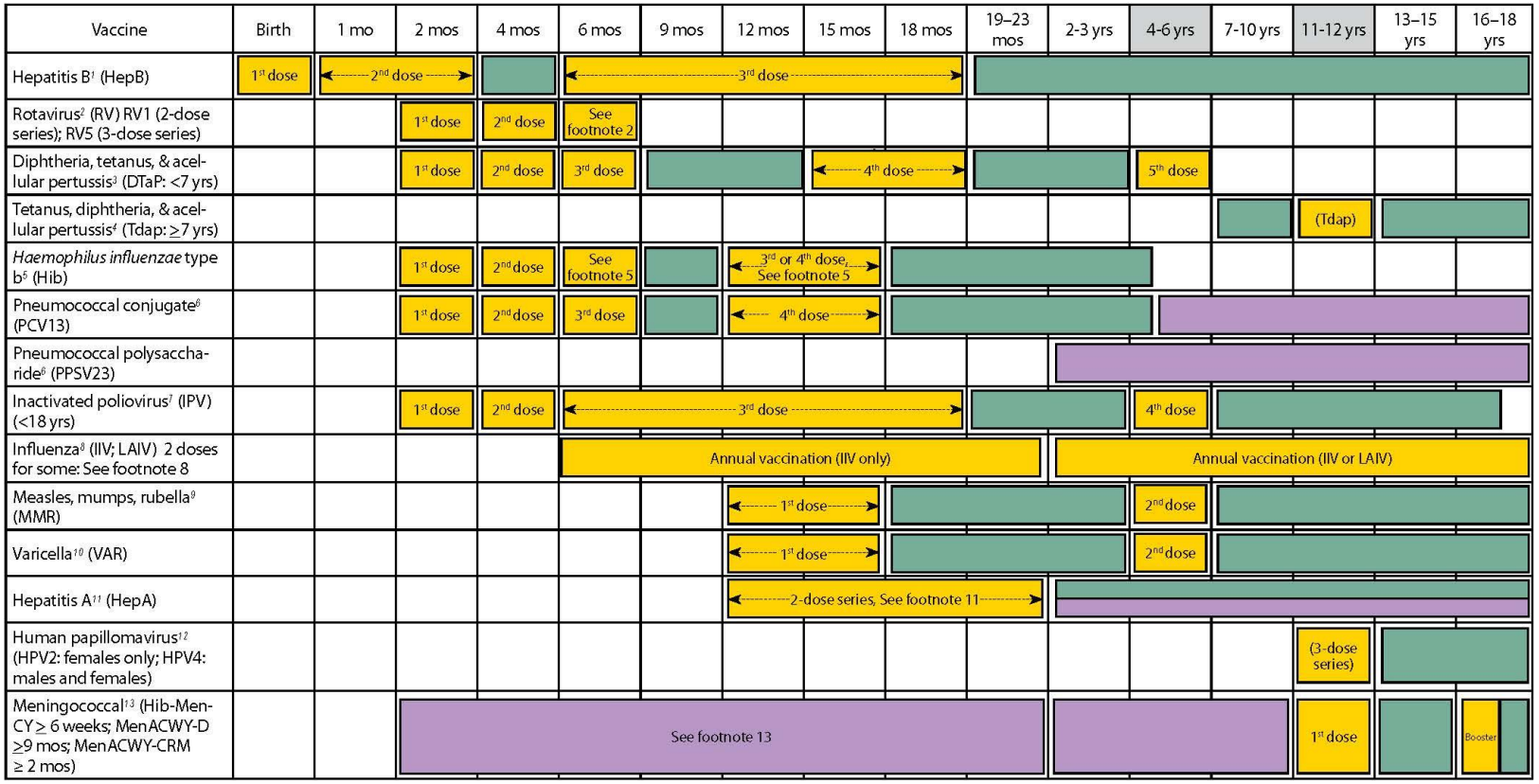
- Multiple licensed vaccine types, with different manufacturing processes
  - Live and inactivated
  - Trivalent and quadrivalent formulations
  - Egg-based, cell-based, recombinant vaccines available

- Use as a medical countermeasure during influenza pandemics

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2014.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.



This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http//www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

One Key Study Question

Same Day vs. Separate Day Vaccination

Mon	Tue	Wed	Thu	Fri
PCV13+IIV				

Mon	Tue	Wed	Thu	Fri
IIV				
				PCV13

IIV= inactivated influenza vaccine

Does one vaccination regimen result in a lower cumulative febrile seizure risk than the other?

Brookings Webinar on Active Medical Product Surveillance

Findings from a Mini-Sentinel Medical Product Assessment: Influenza Vaccines and Risk of Febrile Seizures

Engelberg Center for Health Care Reform
The Brookings Institution
July 21, 2014

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

Alison Tse Kawai, ScD
Harvard Medical School & Harvard Pilgrim Health Care Institute
On Behalf of the Mini-Sentinel PRISM Team
July 21, 2014

Brookings Institution Webinar

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)

  - $AR_{\text{same day TIV + PCV13}} - AR_{\text{separate day TIV + PCV13}} = 7.3$ per 100,000 children
  - 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 insurers that provide claims data

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

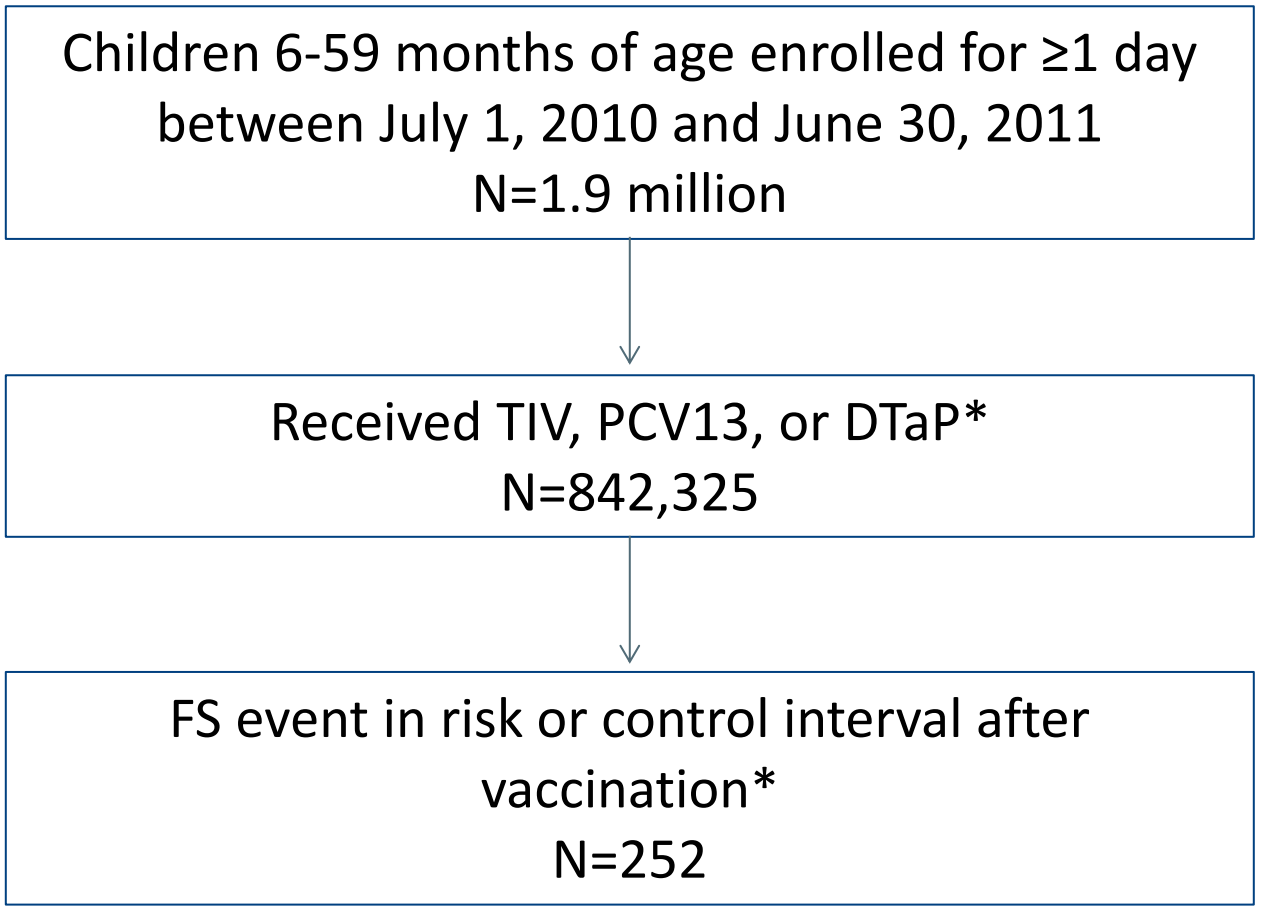
Exposures

- 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

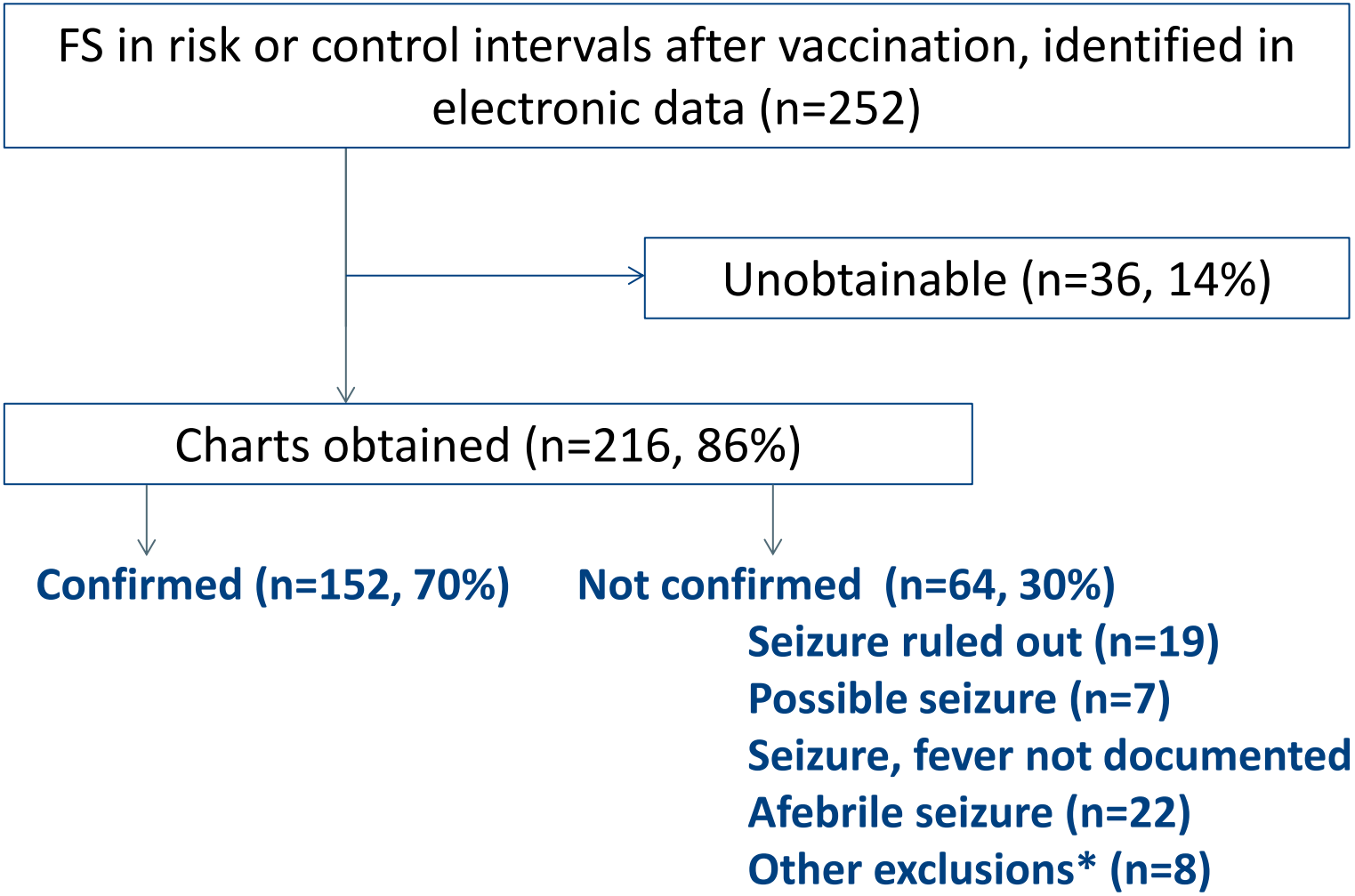
- Outcomes identified in claims data
  - ICD9 codes 780.3, 780.31, 780.32, or 780.39
  - Inpatient and ED settings only
- Validated FS status with medical record review
- Clinician adjudicators confirmed FS
  - Seizure and fever within 24 hours or dx of FS
  - Excluded those w/ conditions in AAP treatment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

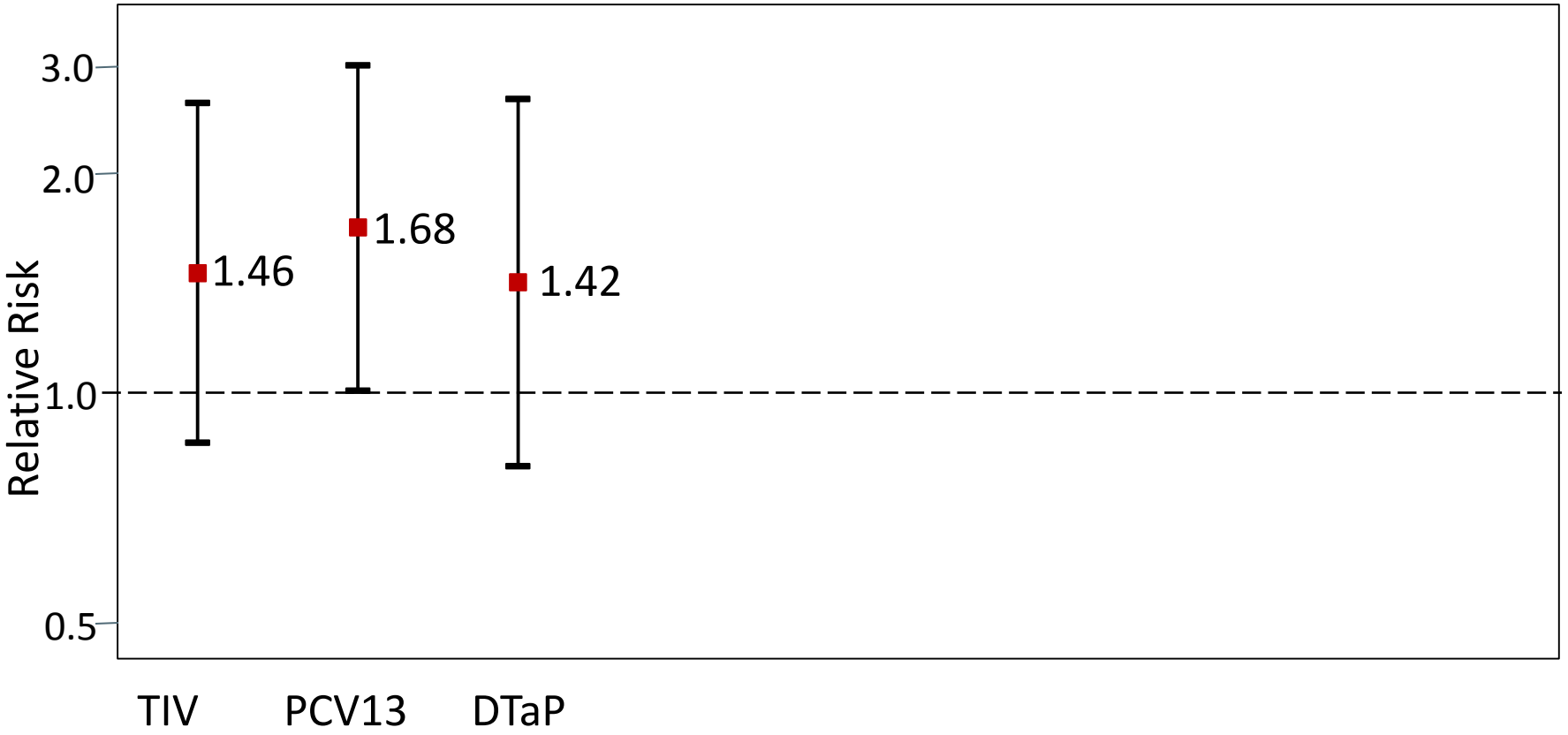
Relative risk and attributable risk estimates

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

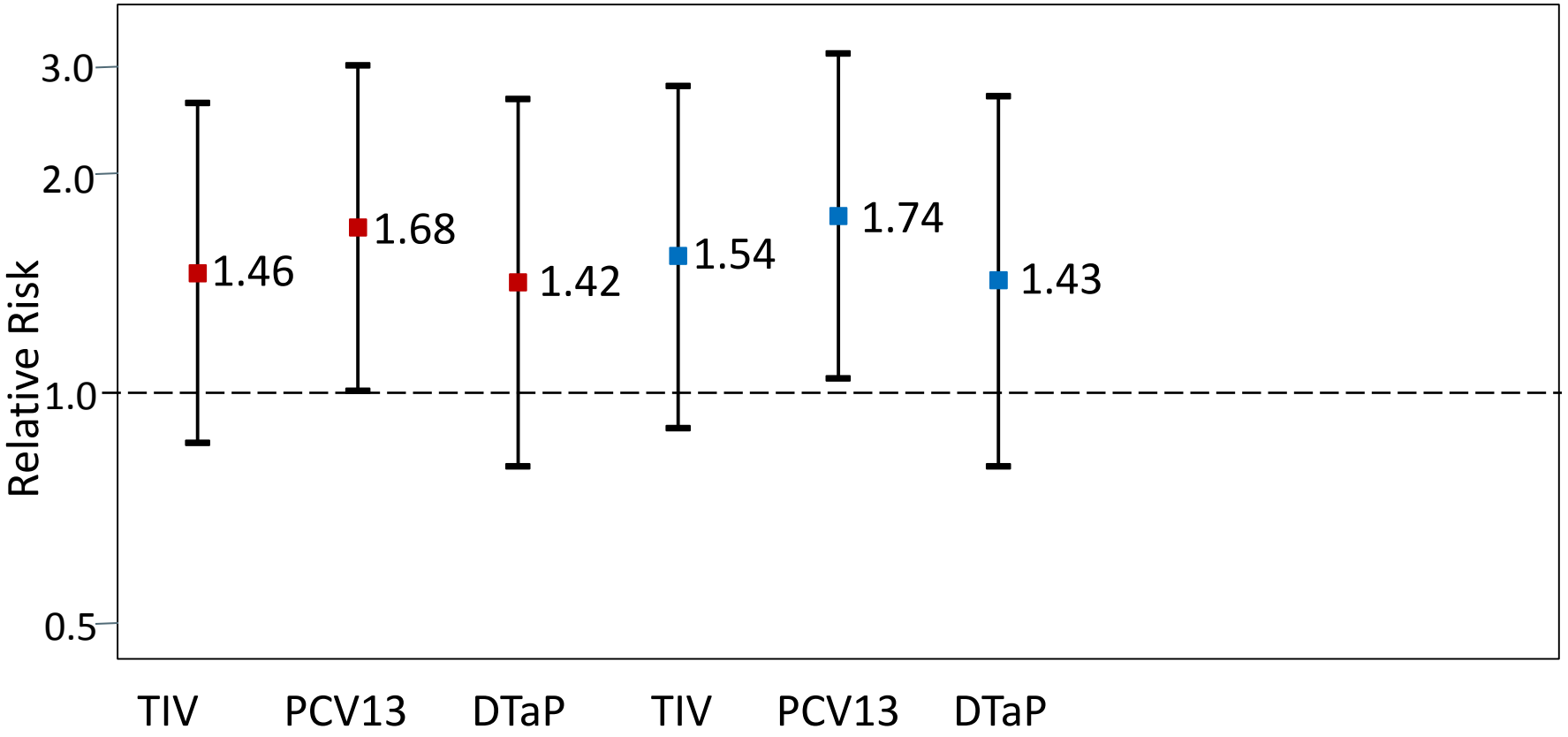
- Age and calendar time adjustments
  - Included person time from underlying PRISM cohort
  - Quadratic splines used to adjust for age and calendar time

Relative Risk Estimates

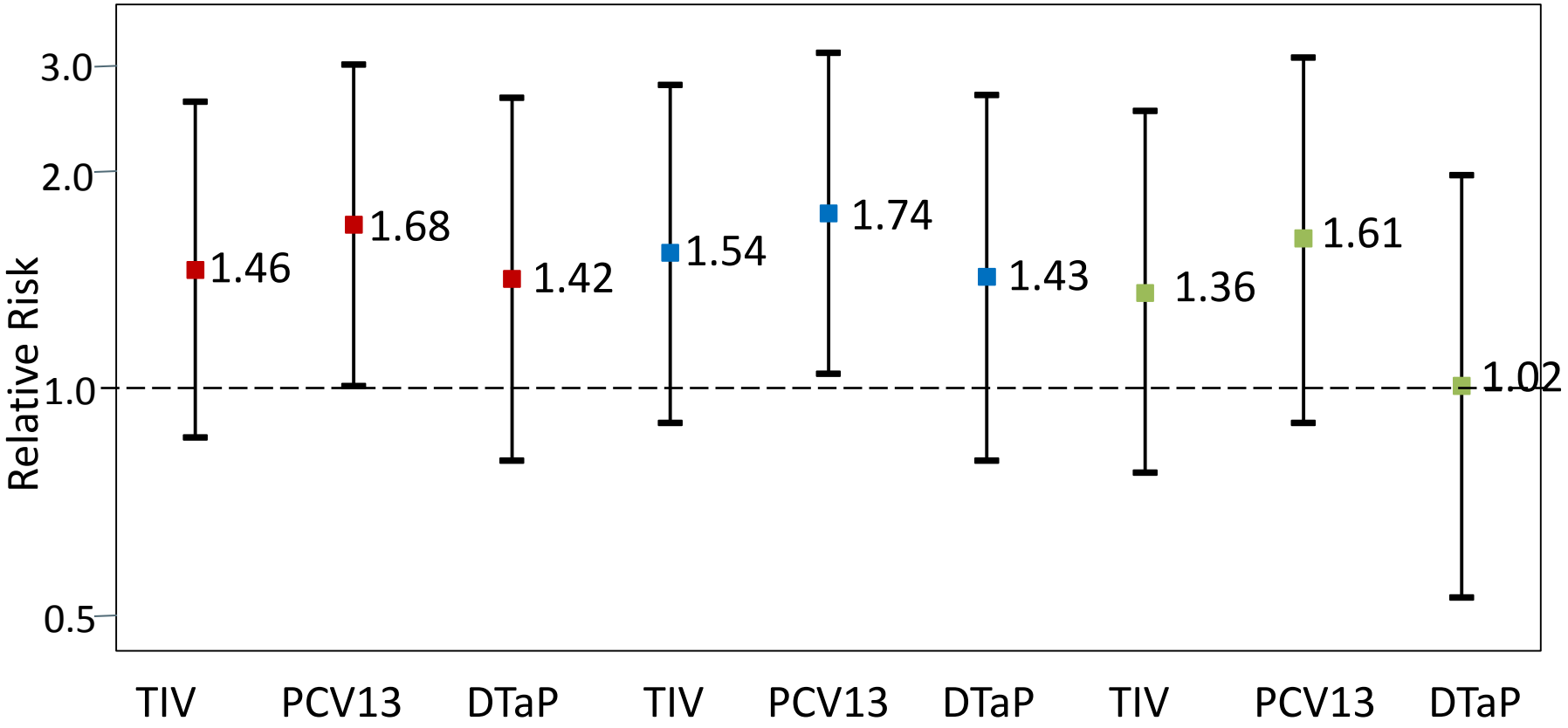


Unadjusted

Relative Risk Estimates



Relative Risk Estimates



Unadjusted

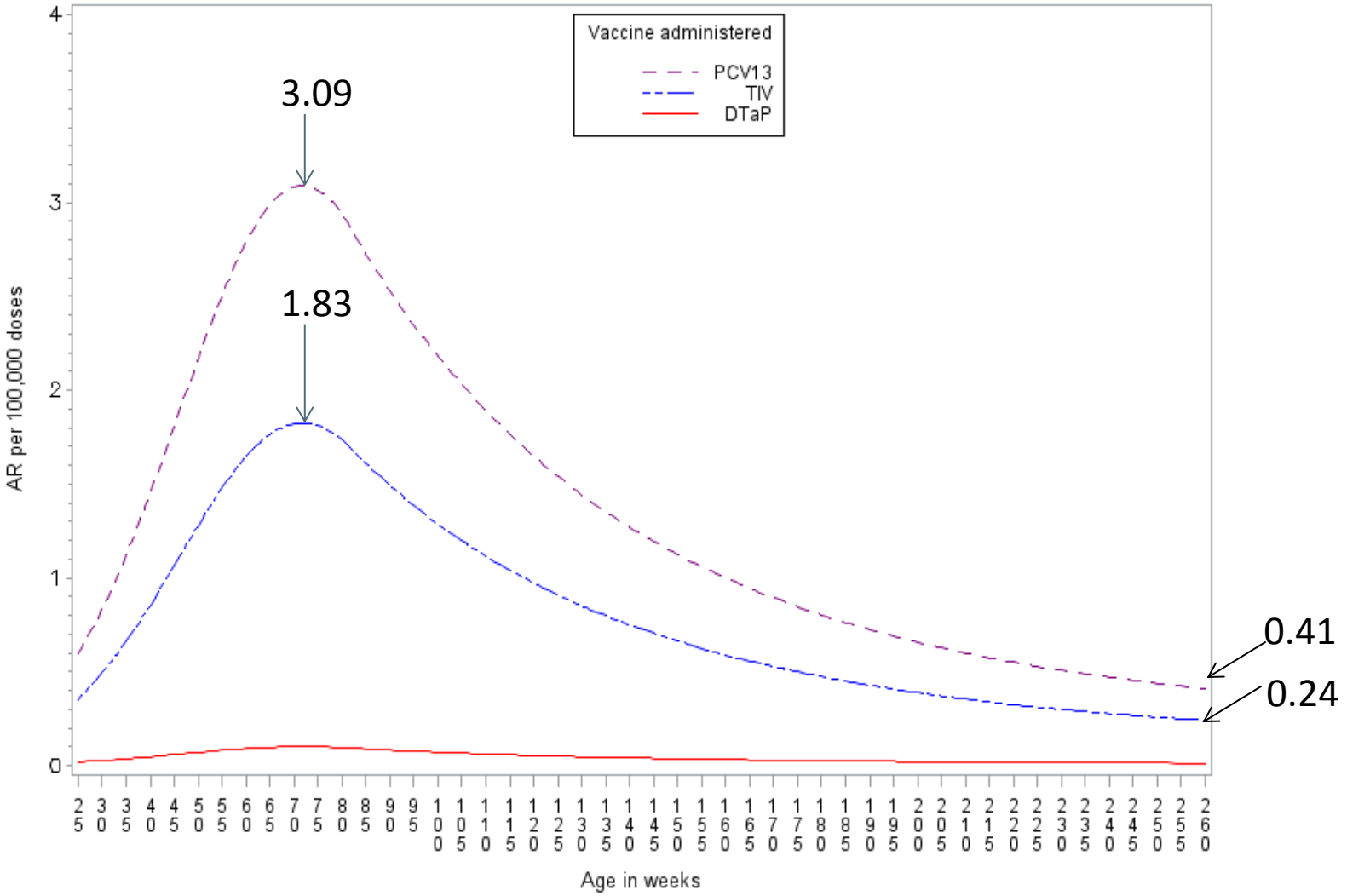
Age & calendar time adjusted

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

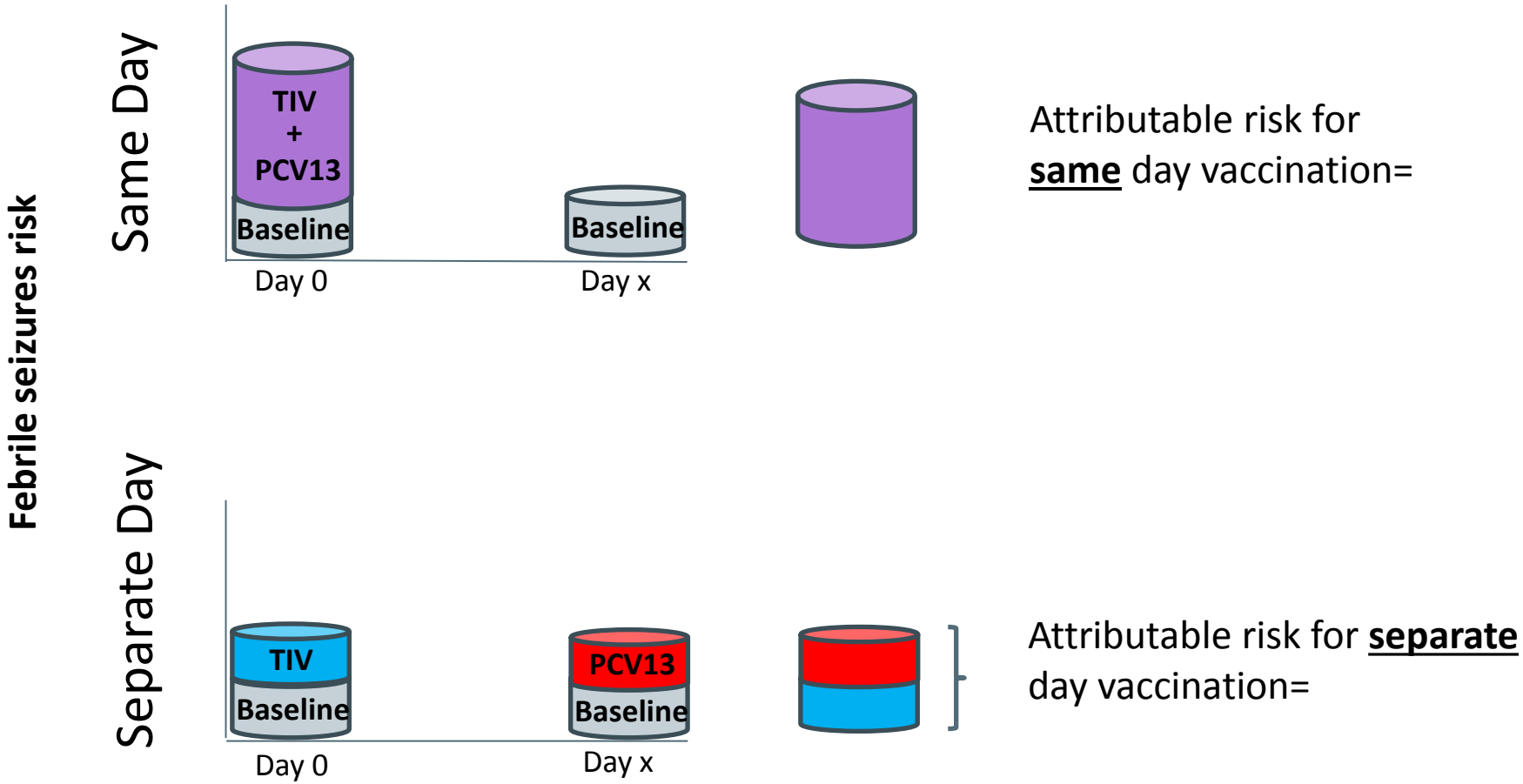
*Baseline risk of FS, 6-59 months of age: 2774.72 per 100,000 children

(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?

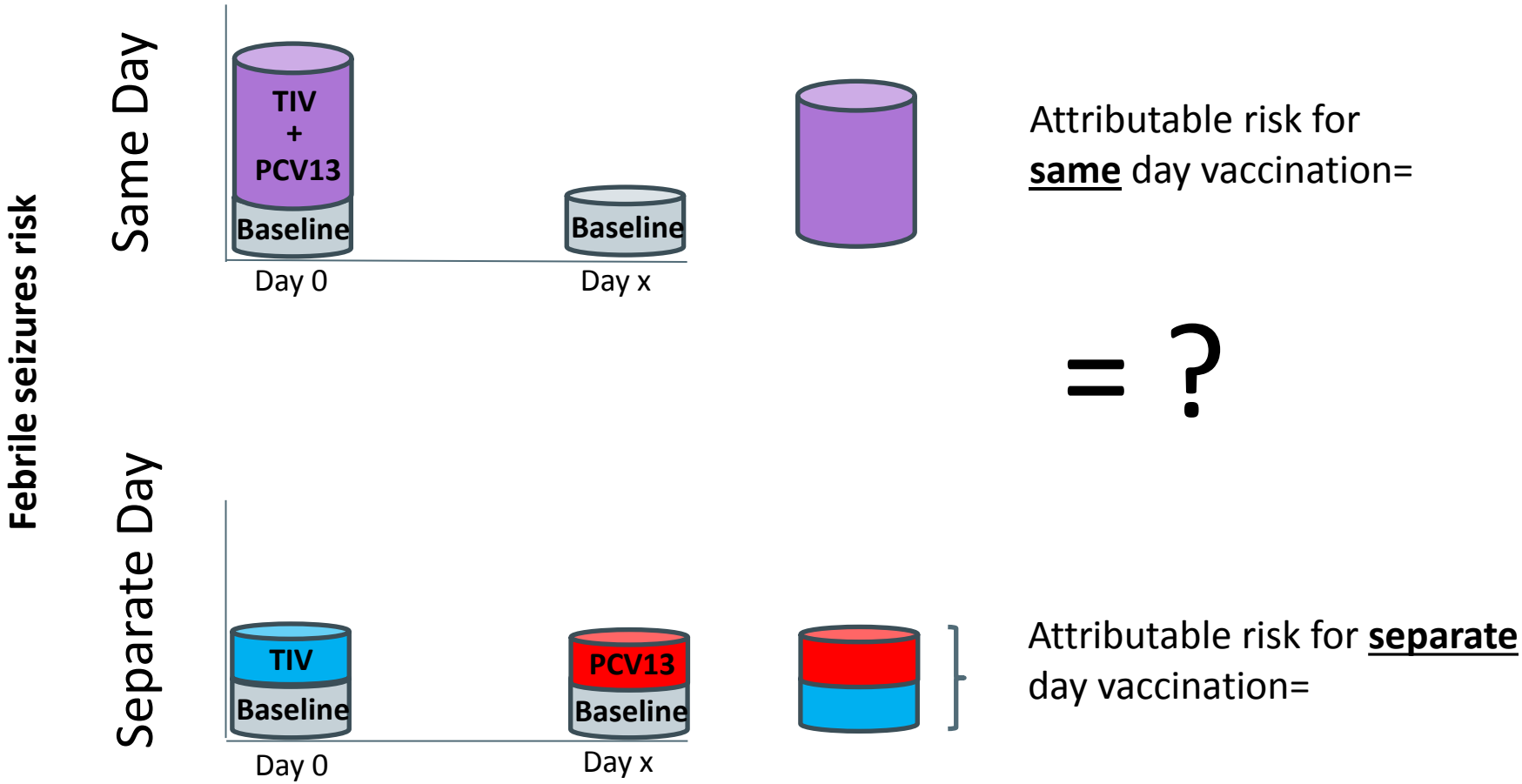
*Difference in attributable risk for same day vaccination vs. that for separate day vaccination**

*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



Same Day Vs. Separate Day TIV + PCV13

- Excess risk associated with same day vs. separate day vaccination= $AR_{TIV + PCV13} - [AR_{TIV} + AR_{PCV13}]$

- AR estimates were derived from IRRs based on conditional Poisson model[†]
  - TIV, PCV13, TIV*PCV13
  - Adjustments for age and seasonality

- 95% CI for difference in ARs estimated using Monte Carlo simulations

[†] AR=(IRR-1)*2*p_0*PPV, where p_0=baseline rate of FS in claims and PPV=positive predictive value of claims codes for FS

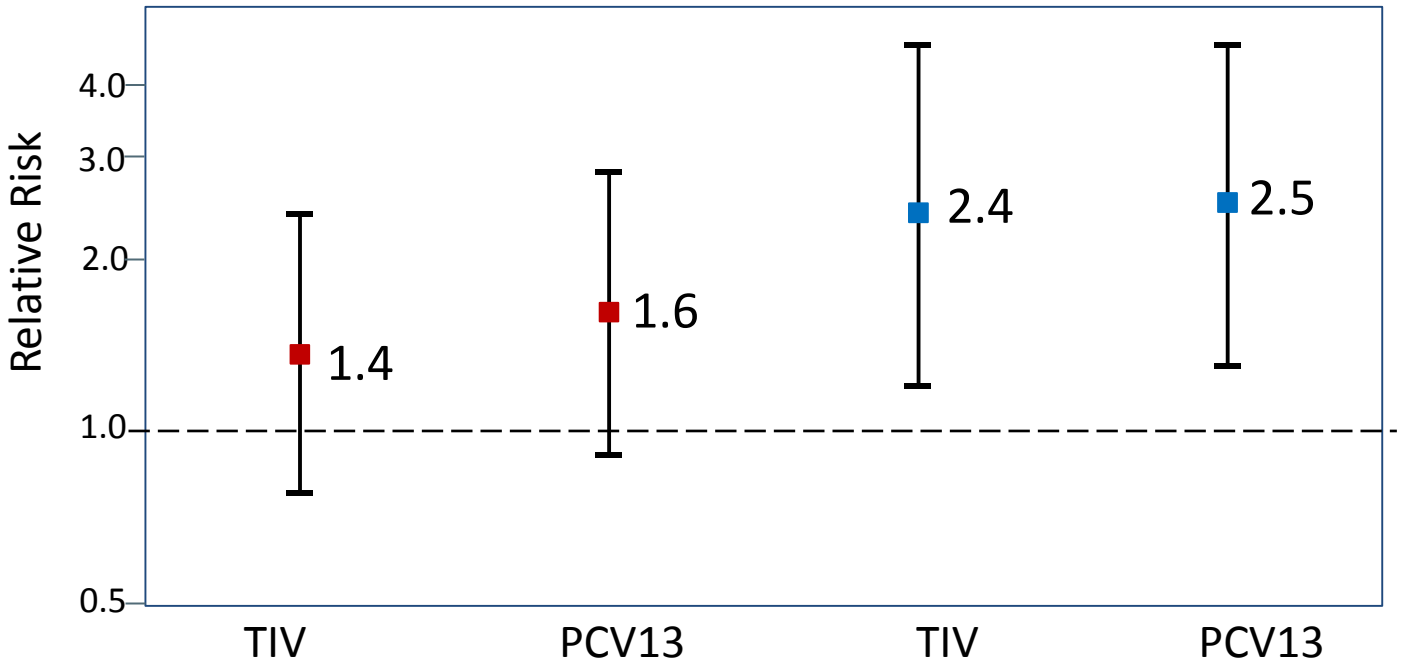
Same Day Vs. Separate Day TIV + PCV13

- 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)

FDA/CBER

Wei Hua

David Martin

Michael Nguyen

Data partners

Aetna

HealthCore

Humana

MS/PRISM team

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

Brookings Webinar on Active Medical Product Surveillance

Findings from a Mini-Sentinel Medical Product Assessment: Influenza Vaccines and Risk of Febrile Seizures

Engelberg Center for Health Care Reform
The Brookings Institution
July 21, 2014