Background and follow-up on the 2010-11 febrile seizure signal for trivalent inactivated influenza and pneumococcal 13-valent conjugate vaccines

Advisory Committee on Immunization Practices
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Tom Shimabukuro, MD, MPH, MBA

Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

Febrile seizures

- "A febrile seizure is a seizure accompanied by fever … without central nervous system infection, that occurs in infants and children 6 through 60 months of age"*
- Febrile seizures are fairly common during childhood; about 2% to 5% of young children will have at least one febrile seizure*
- Febrile seizures can happen with any condition that causes a fever, including typical childhood illnesses, many of which can be prevented by vaccination
- Rarely, febrile seizures can occur after vaccination
- Nearly all children who have a febrile seizure recover quickly and are healthy afterward with no lasting effects
- However, febrile seizures often result in a visit to an emergency room and can be very frightening for parents and caregivers

*Subcommittee on Febrile Seizures; American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389-94.

Post-licensure vaccine safety monitoring infrastructures

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	US frontline spontaneous reporting system to detect potential vaccine safety problems
Vaccine Safety Datalink (VSD)	CDC and health plans	Large linked database system used for active surveillance and research
Clinical Immunization Safety Assessment (CISA) Project	CDC and academic centers	Expert collaboration which conducts individual clinical vaccine safety assessments and clinical research
Post-Licensure Rapid Immunization Safety Monitoring (PRISM)	FDA and health plans	Large linked database system used for active surveillance and research

Definition of a signal in pharmacovigilance

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information."*

*Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action. Geneva, WHO, 2002 (http://apps.who.int/medicinedocs/en/d/Jh2992e/2.html)

Febrile seizures in young children following TIV and PCV13 (background/key events)

2010-11

- VAERS data mining signal for Fluzone®; clinically relevant age group was in children 6-23 mo.*
- VSD Rapid Cycle Analysis (RCA) signal for TIV in children 6-59 mo.
- VSD TIV-PCV13 febrile seizure study**
  - Attributable risk for concomitant TIV+PCV13 peaked at 16 mo. with 45 additional febrile seizures per 100,000 children vaccinated

2011-12

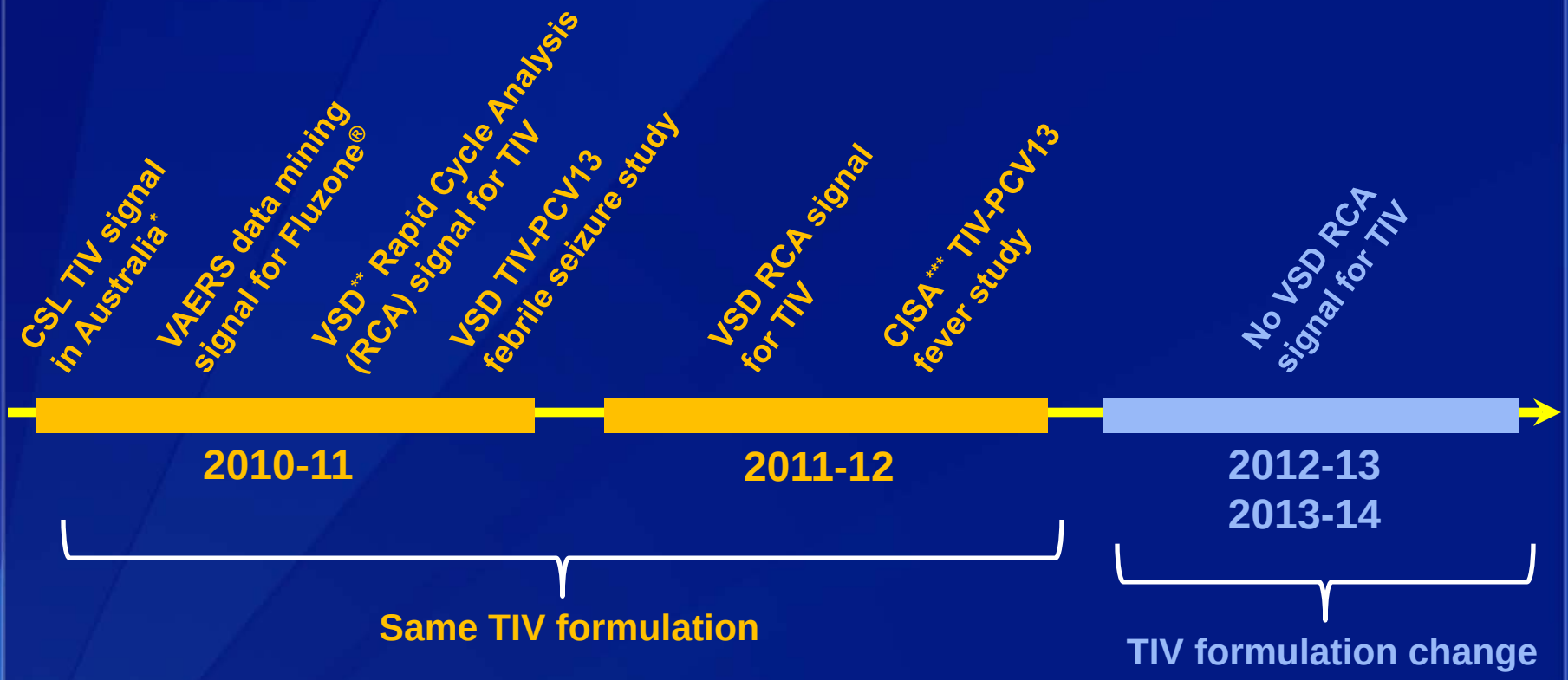
- VSD RCA signal for TIV persisted (same formulation as 2010-11)
- Clinical Immunization Safety Assessment (CISA) Project TIV-PCV13 fever study***
  - Children 6-23 mo. who received TIV and PCV13 together at the same visit were about 3 times as likely to have a fever on days 0-1 compared with children who received TIV or PCV13 without the other product

2012-13
2013-14

- No VSD RCA signal for TIV (formulation change(s) from 2010-11)

*Leroy et al. Vaccine. 2012;30(11):2020-3; **Tse et al. Vaccine. 2012 Mar 2;30(11):2024-31; ***Stockwell et al. JAMA Pediatr. 2014;168(3):211-9

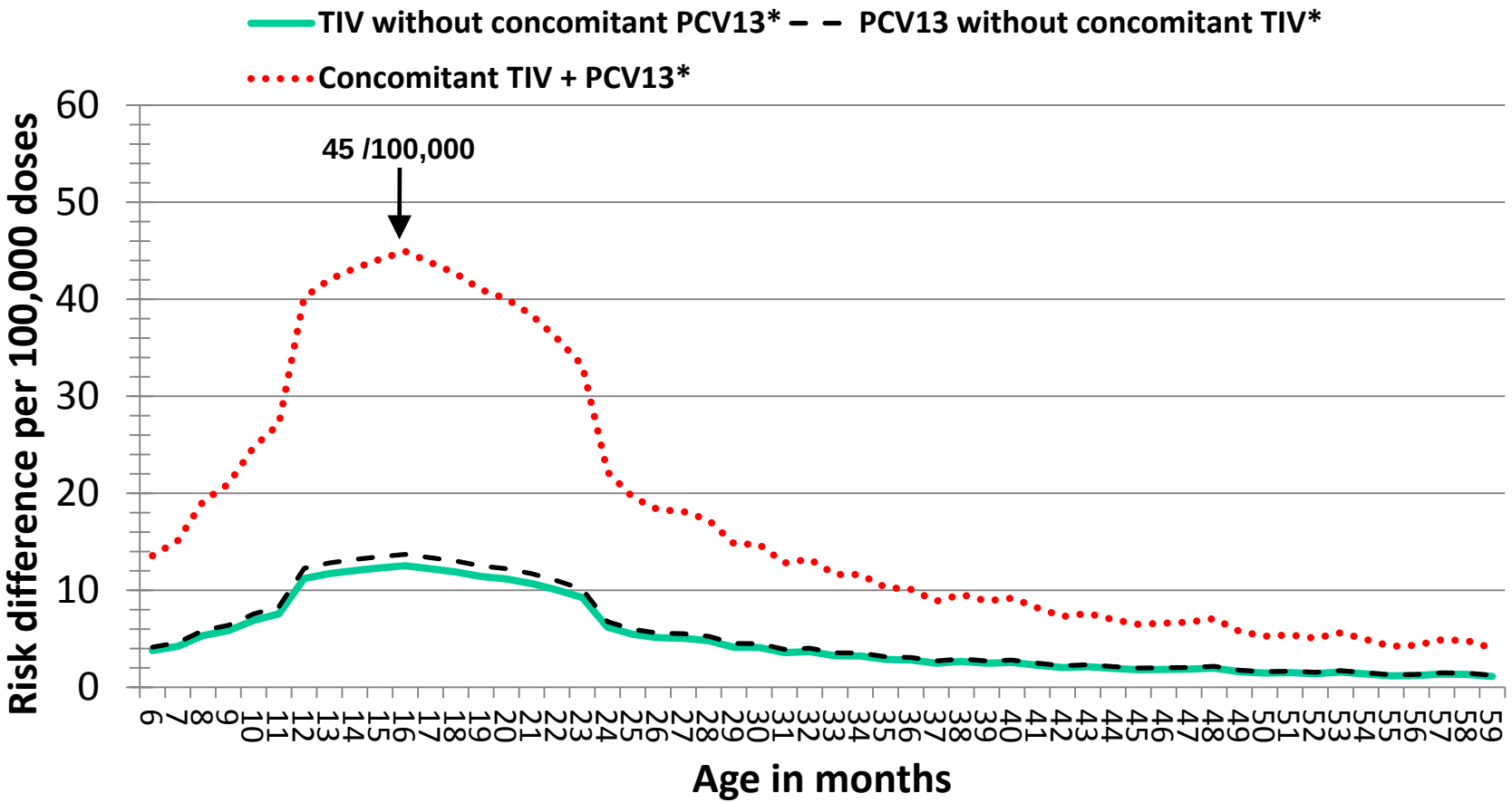
Febrile seizures in young children following TIV and PCV13 (background/key events)



- Signal for febrile seizures following CSL TIV in Australia occurred during the 2010 Southern Hemisphere influenza season, which precedes the US influenza season
- CDC and FDA routinely monitor for febrile seizures following TIV and were alerted to conduct enhanced monitoring in 2010-11 by the Australian experience

* http://www.tga.gov.au/pdf/alerts-medicine-seasonal-flu-100702.pdf; ** Vaccine Safety Datalink; ***Clinical Immunization Safety Assessment Project

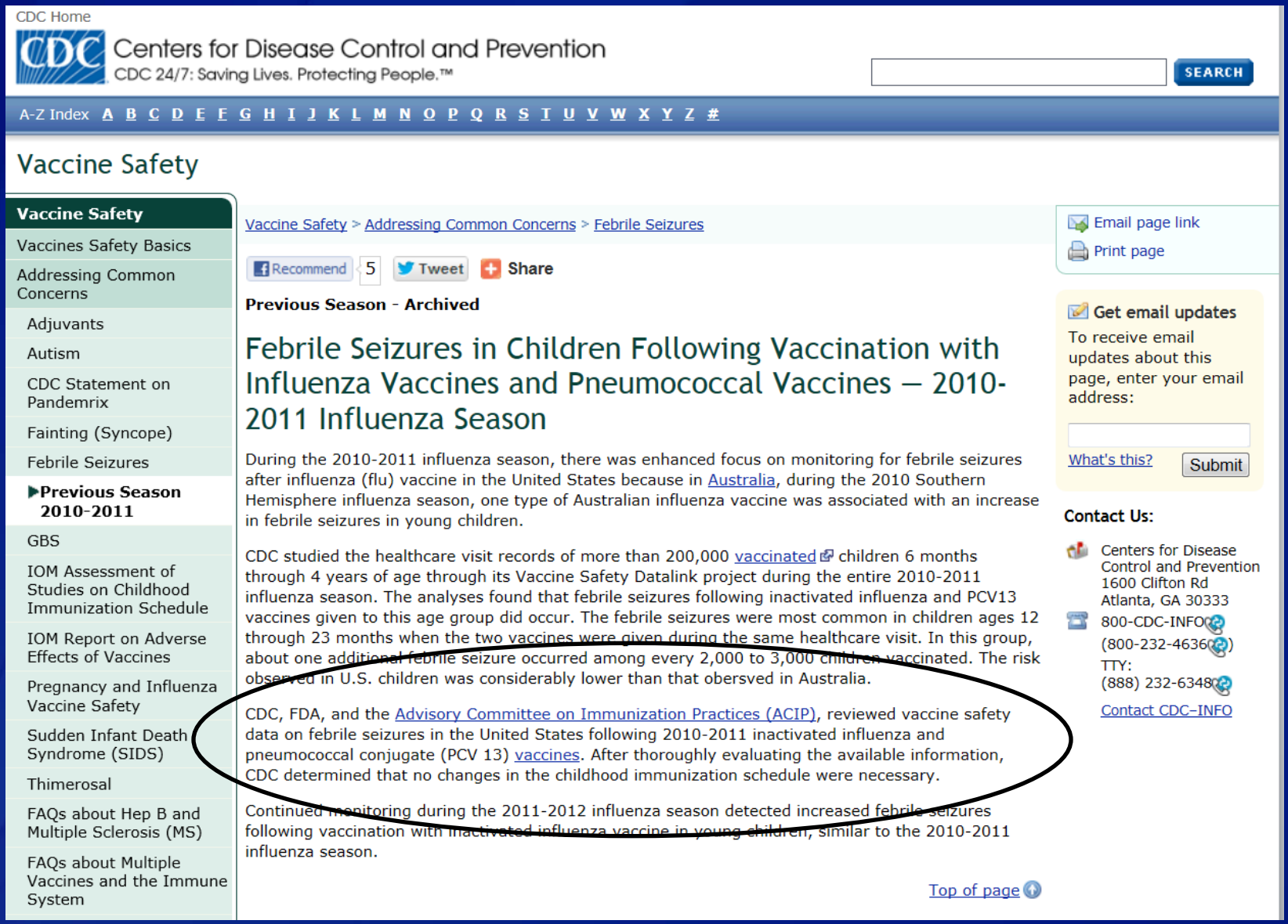
Attributable risk estimates for febrile seizures following 1st dose TIV, 2010-11^



^Adapted from Tse et al. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine. 2012;30(11):2024-31.

*Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines

CDC web posting on febrile seizures following TIV and PCV13*



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Previous Season - Archived

Febrile Seizures in Children Following Vaccination with Influenza Vaccines and Pneumococcal Vaccines — 2010-2011 Influenza Season

During the 2010-2011 influenza season, there was enhanced focus on monitoring for febrile seizures after influenza (flu) vaccine in the United States because in Australia, during the 2010 Southern Hemisphere influenza season, one type of Australian influenza vaccine was associated with an increase in febrile seizures in young children.

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 influenza season. The analyses found that febrile seizures following inactivated influenza and PCV13 vaccines given to this age group did occur. The febrile seizures were most common in children ages 12 through 23 months when the two vaccines were given during the same healthcare visit. In this group, about one additional febrile seizure occurred among every 2,000 to 3,000 children vaccinated. The risk observed in U.S. children was considerably lower than that obersved in Australia.

CDC, FDA, and the Advisory Committee on Immunization Practices (ACIP), reviewed vaccine safety data on febrile seizures in the United States following 2010-2011 inactivated influenza and pneumococcal conjugate (PCV 13) vaccines. After thoroughly evaluating the available information, CDC determined that no changes in the childhood immunization schedule were necessary.

Continued monitoring during the 2011-2012 influenza season detected increased febrile seizures following vaccination with inactivated influenza vaccine in young children, similar to the 2010-2011 influenza season.

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*http://www.cdc.gov/vaccinesafety/Concerns/FebrileSeizures-archived.html

Language added to the inactivated influenza vaccine Vaccine Information Statement (VIS) following the CDC, FDA and ACIP review of the 2010-11 data*

Moderate problems following inactivated flu vaccine:

- Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time may 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.

*http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html

Febrile seizures in young children following TIV and PCV13

- **Questions to follow-up on from the 2010-11 febrile seizure signal**
  - **Did other vaccines besides TIV and PCV13 play any role?**
  - **Was there something unusual about the 2010-11 influenza vaccine that resulted in the increased risk for febrile seizures in young children?**
  - **What do the data prior to the 2010-11 influenza season show?**

Agenda

- "Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study" (Dr. Jonathan Duffy, CDC/ISO)
- "Assessment of febrile seizures after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the Post Licensure Rapid Immunization Monitoring (PRISM) system" (Dr. Alison Kawai, Harvard Medical School and Harvard Pilgrim Health Care Institute)
- Summary (Dr. Tom Shimabukuro, CDC/ISO)
- Discussion

Presentations

Summary

Summary

- **Was the overall risk of febrile seizure increased with the 2010-11 formulation of TIV?**
- **Evidence from published studies includes:**
  - **VAERS signal in 2010-11 for Fluzone®***
  - **VSD Rapid Cycle Analysis (RCA) signal in 2010-11**
    - **Further analysis found a peak attributable risk for concomitant TIV+PCV13 at 16 months of age with 45 additional febrile seizures per 100,000 children vaccinated****
  - **Persistence of the VSD RCA signal for TIV during 2011-12 (same TIV formulation as 2010-11)**
  - **CISA study that found a 3-fold higher rate of fever on days 0-1 when TIV and PCV13 were given together as opposed to separately (2011-12 influenza season, adjusted for other concomitant vaccines including DTaP)*****
- **Above studies could not adequately distinguish the independent risk of febrile seizure associated with TIV alone versus risk with concomitant vaccinations**

*Leroy et al. Vaccine. 2012;30(11):2020-3; **Tse et al. Vaccine. 2012;30(11):2024-31; ***Stockwell et al. JAMA Pediatr. 2014;168(3):211-9.

Summary

- **What was the independent effect of TIV on risk of febrile seizures?**
  - **PRISM analysis* found no statistically significant independent increased risk of febrile seizure associated with TIV during the 2010-11 influenza season**
    - **RR 1.4 (95% CI 0.8, 2.4) in adjusted analysis – TIV adjusted for PCV13 and DTaP**
  - **Updated VSD analysis** found no statistically significant independent increased risk of febrile seizure associated with TIV during the 2010-11 influenza season**
    - **RR 1.2 (95% CI 0.2, 5.8) in stratified analysis – TIV given without PCV13 or DTaP**
  - **Updated VSD analysis** found no independent increased risk of febrile seizure for TIV given without PCV or DTaP during 2006-2009 influenza seasons***

* Kawai. Assessment of febrile seizures after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the Post Licensure Rapid Immunization Monitoring (PRISM) system. June 2014 ACIP meeting.

** Duffy et al. Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study. June 2014 ACIP meeting.

Summary (cont.)

- Was the risk of febrile seizure greater when TIV was given with PCV and/or DTaP?
  - Updated VSD analysis for 2010-11 season suggests that the relative risk increased about 3-fold when TIV was given with PCV and/or DTaP compared with unexposed periods*
    - Similar results seen for the 2006-2009 influenza seasons*
- PRISM analysis did not find any greater risk of febrile seizures for same day vs. separate day vaccination with TIV and PCV13 during the 2010-11 influenza season**

* Duffy et al. Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study. June 2014 ACIP meeting.

** Kawai. Assessment of febrile seizures after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the Post Licensure Rapid Immunization Monitoring (PRISM) system. June 2014 ACIP meeting.

Summary (cont.)

- The weight of the evidence and the consistency of the findings from the VSD analysis over several seasons suggest that:
  - When TIV is given alone, risk of febrile seizure is not increased
  - When TIV is given with PCV and/or DTaP, however, risk of febrile seizure is increased
  - Highest risk is when TIV + PCV + DTaP given together at 15 months of age
    - Attributable risk = 38 additional febrile seizures per 100,000 children vaccinated
    - Similar to febrile seizure risk seen with measles-mumps-rubella (MMR) vaccine*

* Barlow et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001;345(9):656-61.

Conclusion

- Simultaneous administration of TIV with PCV and/or DTaP vaccines appears to be associated with an increased risk for febrile seizures in young children
- This increased risk is transient (the day of to the day after vaccination [days 0-1])
- Although frightening for parents and caregivers, febrile seizures do not have lasting effects
- Getting recommended childhood vaccines during a single healthcare visit has important benefits
  - On-time vaccinations keep children protected against many infectious diseases, and providing multiple vaccinations in a healthcare visit minimizes the number of healthcare visits that parents, caregivers, and children must make

Acknowledgements

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- Martin Kulldorff

Discussion

Centers for Disease Control and Prevention
Atlanta, GA

National Center for Emerging and Zoonotic Infectious Diseases

Division of Healthcare Quality Promotion – Immunization Safety Office

Thank You

For more information please contact Centers for Disease Control and Prevention
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