Timing and Spacing of Immunobiologics: Febrile Seizures and Simultaneous Vaccination

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Febrile Seizures and Simultaneous Vaccination

Febrile Seizures and Simultaneous Vaccination: Background

- Content presented to ACIP in February 2013
- New data presented from Immunization Safety Office in June 2014
- No change in current language

ACIP – February 2013

- Language added to ACIP document to accommodate recognition of attributable risk of febrile seizures with simultaneous vaccination of IIV and PCV13

(Data originally presented to ACIP February 2011)

Language in February 2013

- During the 2010-2011 influenza season, surveillance systems detected safety signals for febrile seizures in young children following TIV and PCV13 vaccines. CDC studied the healthcare visit records of more than 200,000 vaccinated children 6 months through 59 months of age through the Vaccine Safety Datalink Project during the 2010-2011 influenza season. The analyses found that febrile seizures following TIV and PCV13 vaccines given to this age group were rare but did occur at higher than expected rates. The risk for febrile seizures peaked in children age 16 months and were more common when the two vaccines were given during the same healthcare visit. In this group, about one additional febrile seizure occurred among every 2,200 children vaccinated. After assessing benefits and risks, ACIP continues to recommend that TIV and PCV13 be given concomitantly if both are recommended. (Leroy Z, Vaccine 2012)
- (PAGE 5, LINE 18)

Data since February 2013

- VSD observed an increased risk of febrile seizure in young children for IIV in both the 2010-2011 and 2011-2012 influenza seasons (the same IIV formulation was used in both seasons)
- A CISA study found a higher rate of fever in young children (did not study febrile seizure) with simultaneous IIV and PCV13 vaccination vs. children who received TIV or PCV13 without the other product during the 2011-2012 season
- The IIV formulation changed for the 2012-2013 and 2013-2014 seasons and the VSD detected no febrile seizure signal in those seasons
- Retrospective VSD and PRISM studies found no independent increased risk of febrile seizures with IIV after controlling for other simultaneous vaccines
- PRISM found no excess risk when IIV given simultaneously with PCV13
- VSD found an excess risk when IIV given simultaneously with either PCV13 or DTaP vaccines
  - The highest risk was observed when all three vaccines were administered simultaneously (IIV, PCV13, and DTaP)
  - Attributable risk of 38 febrile seizures per 100,000 persons vaccinated

NEXT TOPIC
Contraindications and Precautions: Vaccination During Anesthesia/Surgery/Hospitalization

Contraindications and Precautions: Vaccination During Anesthesia/Surgery/Hospitalization

- **Background**
  - Vaccination can be deferred if someone is acutely moderately or severely ill
  - Centers for Medicare/Medicaid Services (CMS) uses as a performance measure the offering of inactivated influenza vaccine (IIV)
  - Surgery/anesthesia may occur during a hospitalization, with elective procedures
- **February 2013 ACIP**
  - Evidence
    - Indirect – of 20 sources discussing hospitalization, surgery, anesthesia, 15 address immune response, but only 5 the immune response to vaccination (1 systematic review, 1 editorial, 3 letters)
    - Inconsistent - 15 studies that looked at immune response – inconsistent (increase or decrease in immune response varied across studies, or across age groups in single studies)

February 2013 ACIP Meeting:

- Evidence summary:
- *Most studies that have explored the effect of surgery or anesthesia on the immune system were observational, included only infants and children, and were small and indirect, in that they did not look at the immune effect on the response to vaccination specifically. They do not provide convincing evidence that recent anesthesia or surgery significantly affect the response to vaccines.*

February 2013 ACIP Meeting

- Statement:
- *The optimal time for vaccination may be hospital discharge to avoid superimposing any vaccine-induced adverse effects on underlying conditions or avoid confusion in determining the etiology for conditions that occur or are exacerbated during the hospitalization. For patients who are deemed moderately or severely ill at the time of discharge, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.*

Anesthesia/Hospitalization/Surgery – Post-meeting Discussion

- Statement
- ~~*The optimal time for vaccination may be hospital discharge to avoid superimposing any vaccine-induced adverse effects on underlying conditions or avoid confusion in determining the etiology for conditions that occur or are exacerbated during the hospitalization.*~~ *Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.*
- PAGE 20, LINE 26

Precaution – New General Definition

- Presented at February 2013 Meeting
- A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction, might cause diagnostic confusion or that might compromise the ability of the vaccine to produce immunity (PAGE 19, LINE 19)
- (Only change is the underlined content)
- Can be applied to situations involving anesthesia/surgery/hospitalization

NEXT TOPIC
Vaccine Administration: Safe Injection Practices

Vaccine Administration: Safe Injection Practices

- **Preparation and Timely Disposal**

  CDC's Vaccine Safe Injection Practices program

  www.cdc.gov/injectionsafety/

  IP07_standardPrecaution.html

  - Lays out specific information regarding
  - Reinsertion of used needles in multidose vials
  - Where multidose vials can be opened (proximity to patient)
- **CDC Workgroup tasked to harmonize safe injection practices with CDC Administration guidance (including ACIP General Recs)**

Safe Injection Practices

- **Language presented to ACIP at October 2013 meeting**
  - Vaccines should be drawn up in a designated clean medication area that is not adjacent to areas where potentially contaminated items are placed. Multi-dose vials to be used for more than one patient should not be kept or accessed in the immediate patient treatment area. This is to prevent inadvertent contamination of the vial through direct or indirect contact with potentially contaminated surfaces or equipment that could then lead to infections in subsequent patients. If a multi-dose vial enters the immediate patient treatment area, it should be discarded after use. (REF http://www.cdc.gov/injectionsafety/providers/provider_faqs_multivials.html) “

Safe Injection Practices

- Discussion with CDC/NCEZID/DHQP (Safe Injection Practices)
- Must adhere to www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf
- ***Multi-dose vials to be used for more than one patient should not be kept or accessed in the immediate patient treatment area. This is to prevent inadvertent contamination of the vial through direct or indirect contact with potentially contaminated surfaces or equipment that could then lead to infections in subsequent patients.*** ~~*If a multi-dose vial enters the immediate patient treatment area, it should be discarded after use.*~~
- PAGE 34, LINE 26

NEXT TOPIC
Vaccine Administration: Clinical Implications of Non-standard Vaccination Practices

Vaccine Administration: Clinical Implications of Non-standard Vaccination Practices

- **Background**
  - For vaccines approved for intramuscular administration, providers can use the intramuscular route for patients with hemophilia if the bleeding risk is acceptable
  - Some providers might take this to be a license to administer vaccines subcutaneously
  - Should doses count?
- **Evidence**
  - Varies by vaccine

Non-standard Vaccination Practices: Hepatitis B

- Approved for IM use
- Immunogenicity lower if administered in the gluteus (presumably into subcutaneous deep fat) or intradermally
- Studies that show comparable immunogenicity when comparing IM versus subcutaneous performed in hemophiliacs receiving HBIG, vaccine, and at risk for infection by HBV complicating serologic results

Shaw F, Jr., et al, Vaccine 1989;7:425--30.
Redfield RR, et al, JAMA 1985;254:3203--6.
Coleman PJ, et al, Vaccine 1991;9:723--7.
Gazengel C, et al. Scand J Haematol, 1984
Janco RL. J Pediatr, 1985
Zanetti AR, et al. Am J Hematol, 1986
Hedner U, et al. Scand J Haematol, 1984

Non-standard Vaccination Practices: Hepatitis B

- Other studies ongoing to look at immunogenicity of HepB vaccine administered subcutaneously
- Current ACIP recommendation is to repeat the dose

Non-standard Vaccination Practices: Rabies Vaccine

- Approved Intramuscular (one ID vaccine used internationally, not in U.S.)
- Repeat doses administered in the gluteus (presumably into subcutaneous deep fat)

Fishbein DB, et. al, N Eng J Med 1988;318:124--5.

Non-standard Vaccination Practices: Human Papillomavirus Vaccine

- Approved for Intramuscular Injection
- No data to indicate reduced immunogenicity or effectiveness if administered by another route
- General practices is to recommend repeat dosing if administered Subcutaneous (expert opinion)

Non-standard Vaccination Practices: Meningococcal Conjugate Vaccine

- Approved IM
- Polysaccharide vaccine (MPSV4) approved SubCut
- CDC looked at data for subcutaneously administration of MenACWY and found doses to be immunogenic
- CDC does NOT recommend repeating the dose

- CDC. Inadvertent misadministration of meningococcal conjugate vaccine---United States, June--August 2005. MMWR 2006;55:101--7.

Non-standard Vaccination Practices: Hepatitis A Vaccine

- Recommended IM
- Comparable immunogenicity found in children with hemophilia when administered HepA vaccine IM versus subcutaneously
- Baseline anti-HAV negative (all 45 subjects)
- October 2013 ACIP meeting – HAV added to MCV4 for vaccine for which we do NOT recommend repeating the dose

Ragni MV, et. Al.. Hemophilia., 2000

Non-standard Vaccination Practices: Hib Vaccine

- Not discussed at October 2013 ACIP meeting (or later)
- Approved IM
- Study of 20 splenectomized children (one hemophiliac)
- 20 IM doses, 1 subcutaneously doses
- Immunogenicity was comparable
- Hib added to list (PAGE 44, LINE 5)

Vaccine Administration: Clinical Implications of Non-standard Vaccination Practices

- Validating doses (no need to repeat) seems to be supported by evidence (weak) for HepA, Hib, and MenACWY
- Invalidating doses (must repeat) supported by evidence (weak) for HepB and Rabies
- Invalidating doses (must repeat) supported by package insert only for HPV
- No guidance for DTaP, PCV13
- Perhaps a statement needed to address these two vaccines

Vaccine Administration: Clinical Implications of Non-standard Vaccination Practices

- *DTaP and PCV13, like all other vaccines approved for intramuscular use, should be administered by the intramuscular route. However, for DTaP and PCV13, there is no evidence to support repeating doses of these vaccines if given subcutaneously. Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by case basis.*

NEXT TOPIC
Vaccine Information Sources

Vaccine Information Sources

- A listing of organizations with web sites and contact information
- The last section to be reviewed by ACIP
- Will not be voted on today – 2nd half of document
- List of organizations
  - CDC-INFO Contact Center
  - CDC's National Center for Immunization and Respiratory Diseases
  - Morbidity and Mortality Weekly Report (MMWR)
  - American Academy of Pediatrics (AAP)
  - American College of Physicians (ACP)
  - American Academy of Family Physicians (AAFP)
  - Immunization Action Coalition (IAC)
  - National Network for Immunization Information (NNII)
  - Vaccine Education Center (VEC)
  - Institute for Vaccine Safety (IVS)
  - Group on Immunization Education – Society for Teachers of Family Medicine (GIE-STFM)
  - State and Local Health Departments

The ACIP General Recommendations Work Group

- Chair
  - Marietta Vázquez
- CDC-lead
  - Andrew Kroger
- ACIP members
  - Kathleen Harriman
  - Doug Campos-Outcalt
  - Cynthia Pellegrini
- Liaison Representatives
  - Chris Barry (AAPA)
  - Katie Brewer (ANA)
  - Stephen Foster (APhA)
  - Stanley Grogg (AOA)
  - Paul Hunter (AAFP)
  - Shainoor Ismail (Public Health Agency of Canada)
  - Walter Orenstein (AAP, NVAC)
  - Mark Sawyer (PIDS)
  - David Weber (SHEA)
- Consultants
  - William Atkinson
  - Richard Clover
  - Jeff Duchin
  - Susan Lett
  - Kelly Moore
  - Deborah Wexler
  - Rick Zimmerman

Discussion

- Feedback provided by ACIP members on first half of document
- Six replied
- 3/6 – made comments
  - Timing and Spacing, and Tables - Update TIV to IIV – depending on intent
  - Cross reference live vaccines having a potential suppressive effect on Interferon Gamma Release Assay tests for LTBI. (Already in the text, but needs referencing in other parts of the document – tables)
  - Timing and Spacing - Change language to de-emphasize blunting effect of PPSV23 on PCV13, instead emphasize positive priming effect of PCV13 on PPSV23 (document will go through CDC clearance – can be reviewed by DBD)

Unfinished Business
General Recommendations on Immunization

Discussion Points (D.P.) (1, 2a, 2b, 3)

- **Wording presented to ACIP on 10/29/14 that needed some revision**

  1.Contraindications and Precautions

  - Vaccination during anesthesia/surgery/hospitalization

  2.Vaccine Administration

  - Clinical Implications of Non-Standard Vaccination Practices

  2a) Statement regarding subcutaneous administration of vaccines approved by the intramuscular route for which there are no data

  2b) Inclusion of Hib vaccine in above statement

- **Revision shared from ACIP regarding simultaneous vaccination of PCV13 and PPSV23**

  3. Revision to draft language (not presented to ACIP on 10/29/14, but shared with ACIP on 10/10/14)

Contraindications and Precautions: Vaccination During Anesthesia/Surgery/Hospitalization

D.P.1 October 29, 2014 ACIP Meeting

- Evidence summary:
- *Most studies that have explored the effect of surgery or anesthesia on the immune system were observational, included only infants and children, and were small and indirect, in that they did not look at the immune effect on the response to vaccination specifically. They do not provide convincing evidence that recent anesthesia or surgery significantly affect the response to vaccines.*
- (PAGE 20, LINE 21)

D.P.1 October 29, 2014 ACIP Meeting

- *Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.*
- (PAGE 20, LINE 26)

D.P.1 ACIP Concerns 10/29/14

- Providers of patients recently vaccinated may be scheduled for elective surgery
- Some providers already use intervals
- Door needs to be open for some flexibility as to when to vaccinate

D.P.1 ACIP Liaison Concerns 10/29/14

- American Academy of Pediatrics
- Infectious Diseases Society of America
- Current language defining hospitalization/surgery/anesthesia as a precaution might lead to withholding vaccines that can be protective by preventing disease in someone with upcoming surgery
- Concern may be different for different vaccines
- Guidance is needed but cannot be too prohibitive

D.P. 1ACIP GRWG Proposal 10/30/14

- Connect the two passages with a bridging statement about the fact that current, recent, or upcoming anesthesia/surgery/hospitalization is not a contraindication to vaccination.

Proposal for Discussion Point 1

- *Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.* Current, recent, or upcoming anesthesia/surgery/hospitalization is not a contraindication to vaccination*. Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.*

D.P.2a/2b Vaccine Administration Clinical Implications of Non-Standard Vaccination Practices

D.P.2a/2b

- *DTaP and PCV13, like all other vaccines approved for intramuscular use, should be administered by the intramuscular route. However, for DTaP and PCV13, there is no evidence to support repeating doses of these vaccines if given subcutaneously. Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by case basis.*

D.P.2a/2b ACIP Concerns 10/29/14

- D.P.2a Current language: burden on the evidence to demonstrate that doses (DTaP, PCV13) administered subcutaneously need to be repeated
- D.P.2a Can't place the burden on the evidence to demonstrate that doses need to be counted generally (because there is no such evidence for HPV vaccine)
- D.P.2b Cannot group Hib vaccine with Hepatitis A vaccine and MCV4/MenACWY since level of evidence is not met to avoid grouping Hib with DTaP and PCV13
- D.P.2a Neutral language suggested that does not suggest a specific action step

Proposal for Discussion Point 2a/2b, October 30, 2014

- *DTaP , Hib, and PCV13, like all other vaccines approved for intramuscular use, should be administered by the intramuscular route. However, for DTaP , Hib, and PCV13, there is no evidence related to immunogenicity of these three vaccines given subcutaneously. ~~to support repeating doses of these vaccines if given subcutaneously.~~ Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by case basis.*

Proposal for Discussion Point 2a/2b October 30, 2014

- *DTaP , Hib, and PCV13, like all other vaccines approved for intramuscular use, should be administered by the intramuscular route. However, for DTaP , Hib, and PCV13, there is no evidence related to immunogenicity of these three vaccines given subcutaneously. Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by case basis.*

D.P.3 Timing and Spacing of Immunobiologics Simultaneous Administration of PCV13, PPSV23

ACIP Send-out October 10, 2014

- The language states an exception to simultaneous vaccination
- In patients recommended for both PCV13 and PPSV23, the two vaccines should not be administered simultaneously. The immune response to pneumococcal vaccines, particularly PPSV23, stimulates an immune response that inhibits the ability to respond to a follow-up dose of pneumococcal vaccine given shortly thereafter. Because this immune blunting effect is stronger with PPSV23, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. As the immune blunting effect is stronger with PPSV23, if PPSV23 has been administered first, PCV13 should be administered no earlier than one year later.
- PAGE 6, LINE 13

D.P.3 ACIP concerns October 20, 2014

- Received suggestion to emphasize the positive priming effect of PCV13, as opposed to any effect of PPSV23 to blunt the immune response to subsequent doses

D.P.3 ACIP Concerns October 29, 2014

- The ACIP membership wants to see this change before voting
- ACIP GRWG proposal
  - Adopt language from Pneumococcal Vaccine Specific Statement *MMWR*. 2014;63(37);822-825.
  - Needs to flow with the rest of the General Recommendations document

D.P.3 ACIP Presented Language October 29, 2014

- In patients recommended for both PCV13 and PPSV23, the two vaccines should not be administered simultaneously. The immune response to pneumococcal vaccines, particularly PPSV23, stimulates an immune response that inhibits the ability to respond to a follow-up dose of pneumococcal vaccine given shortly thereafter. Because this immune blunting effect is stronger with PPSV23, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. As the immune blunting effect is stronger with PPSV23, if PPSV23 has been administered first, PCV13 should be administered no earlier than one year later.

D.P.3 ACIP GRWG Proposal, October 30, 2014

- In patients recommended for both PCV13 and PPSV23, the two vaccines should not be administered simultaneously. ~~The immune response to pneumococcal vaccines, particularly PPSV23, stimulates an immune response that inhibits the ability to respond to a follow-up dose of pneumococcal vaccine given shortly thereafter. Because this immune blunting effect is stronger with PPSV23, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. As the immune blunting effect is stronger with PPSV23,~~ if PPSV23 has been administered first, PCV13 should be administered no earlier than one year later.

D.P.3 ACIP GRWG Proposal, October 30, 2014

- In patients recommended for both PCV13 and PPSV23, the two vaccines should not be administered simultaneously. Immunogenicity studies evaluating responses to PCV7 and PPSV23 administered in series showed a better immune response when PCV7 was administered first ~~(*9–12*)~~. An evaluation of immune response after a second pneumococcal vaccination administered 1 year after the initial study doses showed that subjects who received PPSV23 as the initial study dose had lower ~~OPA~~ antibody responses after subsequent administration of PCV13 than those who had received PCV13 as the initial dose followed by a dose of PPSV23, regardless of the level of the initial ~~OPA~~ response to PPSV23 ~~(*9*)~~. ~~The immune response to pneumococcal vaccines, particularly PPSV23, stimulates an immune response that inhibits the ability to respond to a follow-up dose of pneumococcal vaccine given shortly thereafter. Because this immune blunting effect is stronger with PPSV23, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. As the immune blunting effect is stronger with PPSV23,~~ PCV13 should be administered first. ~~I~~f PPSV23 has been administered first, PCV13 should be administered no earlier than one year later.

VOTE

- 1st Half of the Document (Today)
- 2nd Half vote in February 2015