General Recommendations on Immunization

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General Recommendations Work Group

CDC

Today: Providing Update on Proposed Revisions for Three Sections

- Timing and Spacing of Immunobiologics
- Contraindications and Precautions
- Special Situations

Timing and Spacing

Timing and Spacing of Immunobiologics

- Clarification on the grace period
- Simultaneous vaccination
  - PCV13 and IIV - febrile seizures
  - PCV13 and MCV4-D

Grace Period

- Applies to sequential doses of the same vaccine in a single series for one patient
- Vaccine can be administered four days short of the minimum age/interval
- Reduces missed opportunities for vaccination
- Immunization Information Systems (IIS) need to catalogue when the Grace Period can be used

Grace Period - Challenge

- The live vaccine rule
- Two different live vaccine components (interferon)
- A new combination vaccine that contains live components
- Components can be given as part of the combination or separately

The Grace Period: MMRV vs. MMR + VAR

- Time One
  - MMR + VAR
- Time Two

The Grace Period: MMRV vs. MMR + VAR

- Time One
  - MMR + VAR
- Time Two
  - MMR

The Grace Period: MMRV vs. MMR + VAR

- Time One
  - MMR + VAR
- Time Two
  - MMR
    - Must be separated from VAR by 28 days – NO GRACE PERIOD – LIVE VACCINE RULE

The Grace Period: MMRV vs. MMR + VAR

- Time One
  - MMR + VAR
  - MMRV
  - VAR
- Time Two
  - MMR
    - Must be separated from VAR by 28 days – NO GRACE PERIOD – LIVE VACCINE RULE

The Grace Period: MMRV vs. MMR + VAR

- Time One
  - MMR + VAR
  - MMRV
  - VAR
- Time Two
  - MMR
    - Must be separated from VAR by 28 days – NO GRACE PERIOD – LIVE VACCINE RULE
  - MMR
    - NO GRACE PERIOD – same rationale

The Grace Period: MMRV vs. MMR + VAR

- Time One
  - MMR + VAR
  - MMRV
  - VAR
- Time Two
  - MMR
    - Must be separated from VAR by 28 days – NO GRACE PERIOD – LIVE VACCINE RULE
  - MMR
    - NO GRACE PERIOD – same rationale
  - MMRV
    - NO GRACE PERIOD – same rationale

Live Vaccine Rule Trumps Grace Period

- Time One
  - MMR + VAR
  - MMRV
- Time Two
  - MMR + VAR
    - NO GRACE PERIOD –
  - MMRV
    - NO GRACE PERIOD –

Grace Period

- Two or more injectable or nasally administered live vaccines not administered on the same day should be separated by at least 4 weeks (Table 3), to minimize the potential risk for interference. If two such vaccines are separated by <4 weeks, the second vaccine administered should not be counted and the dose should be repeated at least 4 weeks later.

- The 4-day grace period discussed earlier, which may be used to shorten the minimum interval between doses of the same vaccine, should not be applied to this 4-week interval between two different live vaccines. Confusion about this prohibition may arise when two live vaccines whose intervals are identical are administered simultaneously. For example, if MMR and varicella vaccines are administered on the same day, the second dose of each vaccine could come due 4 weeks later (depending on the patient's age). If either vaccine had been given alone at both timepoints, the 4-day grace period could be applied to the second dose. But in this situation the live vaccine rule prevents the grace period from being applied to the second dose of either vaccine, because Varicella-2 could potentially be affected by MMR1 if administered earlier than 4 weeks, and MMR-2 could be affected by Varicella-1. Note that this prohibition also applies if the combination MMRV is used rather than individual MMR and varicella vaccines. Live oral vaccines (Ty21a typhoid vaccine and rotavirus) may be administered simultaneously with, or at any interval before or after, any other live vaccines.

- Page 9, Line 1 (P9, L1) of Timing and Spacing

Simultaneous Vaccination TIV and PCV13: Association with Febrile Seizures

- First identification in 2010-2011 influenza season with Fluzone and other vaccines
- Strongest signal linked Fluzone with PCV13
- Febrile seizures are generally benign, and generally do not lead to poor neurologic outcomes
- Invasive pneumococcal disease and influenza cause significant morbidity in infants and toddlers

Simultaneous Vaccination: TIV and PCV13 Vaccination

- We expect one additional febrile seizure for every 2,200 simultaneous vaccinations with IIV and PCV13 in children between 12 and 23 months of age
- ACIP concluded importance of vaccination to prevent pneumococcal and influenza disease outweighed the risks of febrile seizures and made no change in guidance for the immunization schedule or simultaneous administration of these vaccines

Simultaneous Vaccination

- New example where two different vaccines cannot be given simultaneously
- MCV4-D and PCV13 in patients with asplenia
- Interference with PCV13 immune response
- One month interval between PCV13 and MCV4-D
- PCV13 Given First
- (P 4, L14) and (P8, L8), of TIMING AND SPACING)

Contraindications and Precautions

Contraindications and Precautions

- Precaution: vaccination while severely or moderately acutely ill – NEW issue with anesthesia/surgery
- Clarification to Contraindication/precaution tables with respect to history of Arthus reactions

Vaccination While Acutely Ill

- Current general recommendations precaution. Vaccination may be withheld during severe or moderate acute illness
- Challenges: Vaccination during a hospitalization. Centers for Medicare/Medicaid Services (CMS) uses as a performance measure the offering of inactivated influenza vaccine (IIV) and pneumococcal polysaccharide vaccine (PPSV23) during hospitalization
  - This hospitalization may be pre or post – surgery/anesthesia
- Pediatric context: vaccination in the context of elective procedures involving anesthesia (vaccination prior to anesthesia)

General Recommendations Work Group Discussions

- Does there need to be an interval between surgery/anesthesia and vaccination?
- Current ACIP/CDC recommendations/guidance
  - If someone is severely or moderately acutely ill, should defer vaccination until convalescence
  - PCV13, PPSV23, MCV4-D, Hib (provider may give) ideally two weeks before surgery to remove spleen, if feasible

GRWG: Important Outcomes

- Adult context: should a dose of vaccine be withheld following a surgical/anesthesia event? (i.e. is there an interval that should be applied following surgery)
- Pediatric context: should a dose of vaccine be withheld because of upcoming elective surgery? (i.e. is there an interval that should be applied prior to the surgery)
- Primary concern is with efficacy of vaccine

Vaccination and Anesthesia

- 20 papers address hospitalization and the immune response
- Only five address immune response to vaccination with respect to surgery/anesthesia.

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- Puri P, Reen DJ, Browne O, et. Al. Lymphocyte response after surgery in the neonate. Archives of Disease in Childhood. 1979: **54**, 599-603.
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- Kurz R, Pfeiffer P, Sauer H. Immunologic Status in Infants and Children Following Surgery. Infection. 1983. **11**(2), 105-113.
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- Mattila-Vuori A, Salo M, Iisalo E. Immune response in infants undergoing application of cast: comparison of halothane and balanced anesthesia. Can J Anesth. 1999: **46**(11), 1036-1042.
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- Hauser GJ, Chan MM, Casey WF, et. Al. Immune dysfunction in children after corrective surgery for congenital heart disease. Critical Care Medicine. 1991: **19**(7), 874-881.
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- Hansen TG, Tonnesen E, Andersen JB et. Al. The peri-operative cytokine response in infants and young children following major surgery. European Journal of Anesthesiology. 1998: **15**, 56-60.
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- Vuori A, Salo M, Viljanto J, et. Al. Effects of post-operative pain treatment using non-steroidal anti-inflammatory analgesics, opioids or epidural blockade on systemic and local immune responses in children. Acta Anaesthesiol Scand. 2004: **48**, 738-749.
- Siebert JN, Posfay-Barbe KM, Habre W, et. Al. Influence of anesthesia on immune responses and its effect on vaccination in children: review of evidence. Pediatric Anesthesia. 2007: 17, 410-420.
- Currie J. Vaccination: is it a real problem for anesthesia and surgery? Pediatric Anesthesia. 2006: 16, 501-503.
- Siebert J, Posfay-Barbe KM, Habre W, et. Al. Author's Reply. Pediatric Anesthesia. 2007: 17, 1215-1227.
- Nafiu OO, Lewis I. Vaccination and anesthesia: more questions than answers. Pediatric Anesthesia. 2007: 17, 1215-1227.
- Short JA, Van der Walt JH, Zoanetti, DC. Author's Reply. Pediatric Anesthesia. 2007: 17, 1215-1217.

Immune Response to Vaccination and Anesthesia

- Siebert JN, Posfay-Barbe KM, Habre W, et. Al. Influence of anesthesia on immune responses and its effect on vaccination in children: review of evidence. Pediatric Anesthesia. 2007: 17, 410-420.
- Currie J. Vaccination: is it a real problem for anesthesia and surgery? Pediatric Anesthesia. 2006: 16, 501-503.
- Siebert J, Posfay-Barbe KM, Habre W, et. Al. Author's Reply. Pediatric Anesthesia. 2007: 17, 1215-1227.
- Nafiu OO, Lewis I. Vaccination and anesthesia: more questions than answers. Pediatric Anesthesia. 2007: 17, 1215-1227.
- Short JA, Van der Walt JH, Zoanetti, DC. Author's Reply. Pediatric Anesthesia. 2007: 17, 1215-1217.

- One Systematic Review
- One editorial
- Three letters

- NO RANDOMIZED CONTROL TRIALS

- Review article cites provider surveys and studies of surgery/anesthesia and effects on immune parameters, NOT immune response to vaccination

Interval After Anesthesia/Surgery and a Dose of Vaccine (Efficacy)

- Remaining 15 articles
- Address anesthesia and the immune response, but not immune response to vaccination
- 2 Randomized controlled trials (RCT) address anesthesia and the immune response (generally, not to vaccination)

Mattila-Vuori A, Salo M, Iisalo E. Immune response in infants undergoing application of cast: comparison of halothane and balanced anesthesia. Can J Anesth. 1999: **46**(11), 1036-1042.

Vuori A, Salo M, Viljanto J, et. Al. Effects of post-operative pain treatment using non-steroidal anti-inflammatory analgesics, opioids or epidural blockade on systemic and local immune responses in children. Acta Anaesthesiol Scand. 2004: **48**, 738-749.

Strength of Evidence

- Evidence is weak, imprecise (small sample size), indirect (immune response but not to vaccination, different age groups) and inconsistent

- 6 studies looked at both infants and children
  - 3 studies, increase in immune cell numbers in both age groups
  - 1 study showed decrease in immune cell numbers
  - 2 studies showed a decrease in immune cell numbers for infants and an increase in immune cell numbers for children

- 11 studies looked at more than one parameter (antibodies, T-cells)

  8 show variation among parameters

  3 do not show variation

  1 decrease in lymphoproliferation (ConA and PWM)

  1 no change in PMN chemotaxis and actin polymeration

  1 increase PMN phagocytosis and oxidative burst

Strength of Evidence

No evidence to recommend a specific interval otherwise

Current recommendation is to defer vaccination while severely or moderately acutely ill

Discretion of provider

Preferable to vaccinate AFTER anesthesia/surgery as opposed to before

- It is reasonable to vaccinate patients during hospitalization if they are not acutely ill. Health-care facilities are held to standards of offering influenza vaccine for hospitalized patients, so providers are incentivized to vaccinate these patients at some point during hospitalization. Likewise patients admitted for elective procedures will not be acutely ill during all times during their hospitalization. The hospitalization should be used as an opportunity to provide recommended vaccinations. Most studies that explore the effect of surgery or anesthesia on the immune system consist primarily of observational studies, are small, and are indirect in that they do not look at the immune effect on the response to vaccination specifically. Studies that examine the effect of anesthesia on the response to vaccination consist only of a systematic review and expert opinion pieces which vary on the need for or duration of an interval. 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.

- (P2, L18) of "Contraindications and Precautions"

Guillain-Barré Syndrome

- **Multifactorial cause**
- **ACIP recommendations**
  - A history of Guillain-Barré syndrome within 6 weeks of a dose of influenza vaccine or tetanus-toxoid containing vaccine is a precaution to influenza vaccine or tetanus-toxoid vaccine respectively.
  - June, 2010, CDC ACIP Gen Rec WG tasked with determination if precaution can or should be applied more broadly

Guillain-Barré Syndrome

- **Immunization Safety Office and Clinical Immunization Safety Assessment (CISA) Review**
- **Data suggest past history of GBS not a risk for recurrent GBS following vaccination**
  - 279 individuals who experienced GBS previously, 25 experienced GBS following a previous dose of vaccine,
  - 25 experienced previous dose of vaccine, zero experienced GBS following a current dose of vaccine

Baxter, R, CID 2012

Summary of CISA Suggestions

1. Add data from Baxter et al paper (CID, 2012) to the ACIP recommendations for influenza vaccine, stating that these data are reassuring, although the power is limited given the rarity of the condition.
2. Use similar and parallel language regarding recurrence of GBS following both tetanus and influenza vaccines, since these vaccines are the only ones associated with possible recurrence.
3. The experts in the group were comfortable that meningococcal vaccine should no longer be mentioned as a risk factor for recurrent GBS.

Summary of CISA Suggestions

4. Include clear language in the relevant ACIP recommendation documents stating that there is little evidence to support a problem with GBS recurrence after tetanus/influenza vaccination, yet it cannot be ruled out.
5. Be explicit in the general recommendation about guidance for vaccination of persons with a history of GBS
   - Precautions only apply if the GBS occurred within 6 weeks of influenza or tetanus-containing vaccine administration.
   - No precaution to any other vaccine for patients with history of GBS.

Change in Draft Contraindications and Precautions (P10)

TABLE 7. Conditions Incorrectly Perceived as Contraindications to Vaccination (vaccines may be given under these conditions)
Conditions commonly misperceived as contraindications (i.e., vaccination may be administered under these conditions)
Mild acute illness with or without fever
Mild-to-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose
Lack of previous physical examination in well-appearing person
Current antimicrobial therapy*
Convalescent phase of illness
Preterm birth (hepatitis B vaccine is an exception in certain circumstances)†
Recent exposure to an infectious disease
History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
History of Guillain-Barré syndrome§§

§§§§An exception is Guillain-Barré syndrome within six weeks of a dose of influenza vaccine or tetanus-toxoid containing vaccine, which are precautions for influenza vaccines and tetanus-toxoid containing vaccines, respectively.

Arthus Reactions

- Revision to Contraindications and Precaution table for tetanus-toxoid containing vaccines
- Arthus reactions
  - Type III hypersensitivity reaction
  - Circulating/local antigen-antibody complexes
  - Severe local pain, severe erythema, sometimes local necrosis

Arthus Reactions

- Used language from Tdap vaccine specific statement
- MMWR March 24, 2006
- History of arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid—containing or tetanus toxoid--containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine
- Addition of "diphtheria toxoid-containing"

Special Situations

- Vaccination During Pregnancy
- Persons Vaccinated Outside the United States

Vaccinating During Pregnancy

- Need to incorporate new Tdap in pregnancy recommendations
- Administer Tdap during pregnancy regardless of previous Tdap vaccination
- Specific language will trail the language in the Tdap recs, which will be published first

Persons Vaccinated Outside the United States

- Originally dealt with Internationally Adopted Children
- In 2006 broadened to include all persons vaccinated outside the United States
- At issue are persons with records, but the RECORDS ARE UNCERTAIN

Persons Vaccinated Outside the United States

- Uncertain Records
  - Use of tetanus or diphtheria serology as a proxy for pertussis protection
  - In General Recs since 2002
  - With rising numbers of pertussis cases in U.S., is this still appropriate
  - Few countries use DT vaccine, so deemed to be still appropriate
  - http://apps.who.int/immunization_monitoring/en/globalsummary/diseaseselect.cfm

Persons Vaccinated Outside the U.S.

- Uncertain Records
  - Self-report for influenza vaccine and pneumococcal polysaccharide vaccine
  - Self-report already is applied generally to U.S. population for these two vaccines (Timing and Spacing (P12, L14))
  - Rationale for self-report (generally)
    - Influenza – memory lasts one year
    - Pneumococcal polysaccharide vaccine – high rate of adverse reactions if doses given at less than a five year interval

Persons Vaccinated Outside the U.S.

- ONLY removing pneumococcal polysaccharide vaccine from the "self-report" list for persons vaccinated outside of the U.S. (P9, L39 of "special situations")