Intervals Between PCV13 and PPSV23 Vaccines: Evidence Supporting Currently Recommended Intervals and Proposed Changes

Miwako Kobayashi, MD, MPH
EIS Officer
RDB, NCIRD, CDC

Advisory Committee on Immunization Practices

June 25, 2015

Introduction

- Currently, two types of pneumococcal vaccines are being used in the U.S.
  - 13-valent pneumococcal conjugate vaccine (PCV13)
  - 23-valent pneumococcal polysaccharide vaccine (PPSV23)
- Both are recommended for individuals aged ≥2 years with underlying conditions, and all adults ≥65 years
  - Recommended sequence: PCV13 → PPSV23
- Recommended intervals between the two vaccines are not consistent across groups

Currently Recommended Intervals Between the Two Pneumococcal Vaccines

Age groups	Underlying conditions	PCV13 → PPSV23	PPSV23 → PCV13
24–71mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥8 weeks
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥8 weeks
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
≥65 years	NA	6–12 months (minimum 8 weeks)	≥1 year

MMWR September 19, 2014 / 63(37);822-825; MMWR October 12, 2012, Vol 61, #40; MMWR June 28, 2013 / 62(25);521-524; MMWR December 10, 2010 / 59(RR11);1-18

Question Considered by Pneumococcal Work Group

- Would existing data allow harmonization of intervals between:

  PCV13 → PPSV23

  and

  PPSV23 → PCV13

  across age and risk groups?

Outline

- **Harmonizing intervals for PCV13 → PPSV23**
  - Current recommendations
  - Considerations for harmonization
  - Proposed changes for adults aged ≥65 years for routine administration
- **Harmonizing intervals for PPSV23 → PCV13**
  - Current recommendations
  - Considerations for harmonization
  - Proposed changes for children 2–18 years with underlying conditions
- **ACIP vote**

HARMONIZING INTERVALS FOR PCV13 → PPSV23

Currently Recommended Intervals Between PCV13 → PPSV23

Age groups	Underlying conditions	Current interval recommendations
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
≥65 years	NA	6–12 months (minimum 8 weeks)

MMWR September 19, 2014 / 63(37);822-825; MMWR October 12, 2012, Vol 61, #40; MMWR June 28, 2013 / 62(25);521-524; MMWR December 10, 2010 / 59(RR11);1-18; MMWR June 28, 2013 / 62(25);521-524

Current and Proposed Intervals Between PCV13 → PPSV23

Age groups	Underlying conditions	Interval Recommendations	
		Current	Proposed
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	No change
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	No change
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	No change
≥65 years	NA	6–12 months (minimum 8 weeks)	?

MMWR September 19, 2014 / 63(37);822-825; MMWR October 12, 2012, Vol 61, #40; MMWR June 28, 2013 / 62(25);521-524; MMWR December 10, 2010 / 59(RR11);1-18; MMWR June 28, 2013 / 62(25);521-524

Current and Proposed Intervals for Adults Aged ≥65 Years

	PCV13 → PPSV23	PPSV23 → PCV13
Current	6–12 months (minimum 8 weeks)	≥1 year
Proposed	≥1 year	≥1 year

Considerations for Harmonizing Intervals Among Adults Aged ≥65 Years

- Implementation and programmatic challenges
- Immunogenicity studies
- Risk window for PPSV23-only serotypes

Implementation and Programmatic Challenges

- Confusion among healthcare providers
- Challenges in programming reminders in computerized programs
- CMS policy[1]
  - Medicare will cover "*a different, second pneumococcal vaccine one year after the first vaccine was administered (that is, 11 full months have passed following the month in which the last pneumococcal vaccine was administered*".

1. Department of health and human services, 2014
http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/MM9051.pdf

Considerations for Harmonizing Intervals Among Adults Aged ≥65 Years

- Implementation and programmatic challenges
- Immunogenicity studies
- Risk window for PPSV23-only serotypes

Does Evidence Support the Change of the Interval for PCV13 → PPSV23 to ≥1 Year for Adults Aged ≥65 Years?

- No clinical efficacy data to guide selection of intervals for the sequence of PCV13 → PPSV23
- Limited immunogenicity evidence available
  - Direct comparison of intervals available from one study
  - The rest of studies have compared:
    - PCV* → PPSV23 versus PPSV23
    - PCV* → PPSV23 versus PCV*
  - Is there an association between the interval in PCV → PPSV23 series and immune response compared to a single PCV or PPSV23 dose?

*Includes studies that used either PCV7 or PCV13

Summary of Immunogenicity Studies Comparing PCV → PPSV23 vs. PCV Alone in Older Adults

Interval	Difference in immune response after PCV → PPSV23 compared to single PCV dose
6 months	Equivalent for all types[1] Equivalent (5/7 serotypes) or greater (2/7 serotypes)[2]
1 year	Non-inferior (8/12 serotypes) or greater (1/12 serotype)*[3]
3.3–3.9 years	Non-inferior (4/13 types) or greater (7/12 serotypes)*[4]

[1] Musher, JID 2008

[2] Goldblatt, CID 2009

[3] Greenberg, Vaccine 2014

[4] Jackson, Vaccine 2013

*Designed to assess for non-inferiority

Summary of Immunogenicity Studies Comparing PCV → PPSV23 vs. PPSV23 Alone in Older Adults

Interval	Difference in immune response after PCV → PPSV23 compared to single PPSV23 dose
2 months	Equivalent[1]
6 months	Equivalent[1,2] Equivalent (5/9 serotypes) or greater (4/9 serotypes)[3]
1 year	Equivalent (1/7 serotype) or greater (6/7 serotypes)[4]

[1] Miernyk, CID 2008

[2] Lazarus, CID 2011

[3] MacIntyre, PLOS ONE 2014

[4] de Roux, CID 2008

Direct Comparison of Intervals

- **Target population:**
  - Alaska native adults aged 55–70 years, vaccine naïve
- **Comparison:**
  - Group 1: PPSV23 only
  - Group 2: PCV7 → PPSV23 (2 months apart)
  - Group 3: PCV7 → PPSV23 (6 months apart)
- **Outcome measurements:**
  - IgG concentrations and OPA
- **Results:**
  - No difference in immunogenicity among the 3 groups
  - More injection site swelling in the 2 month interval group

Miernyk et al. CID 2008

Summary of Evidence

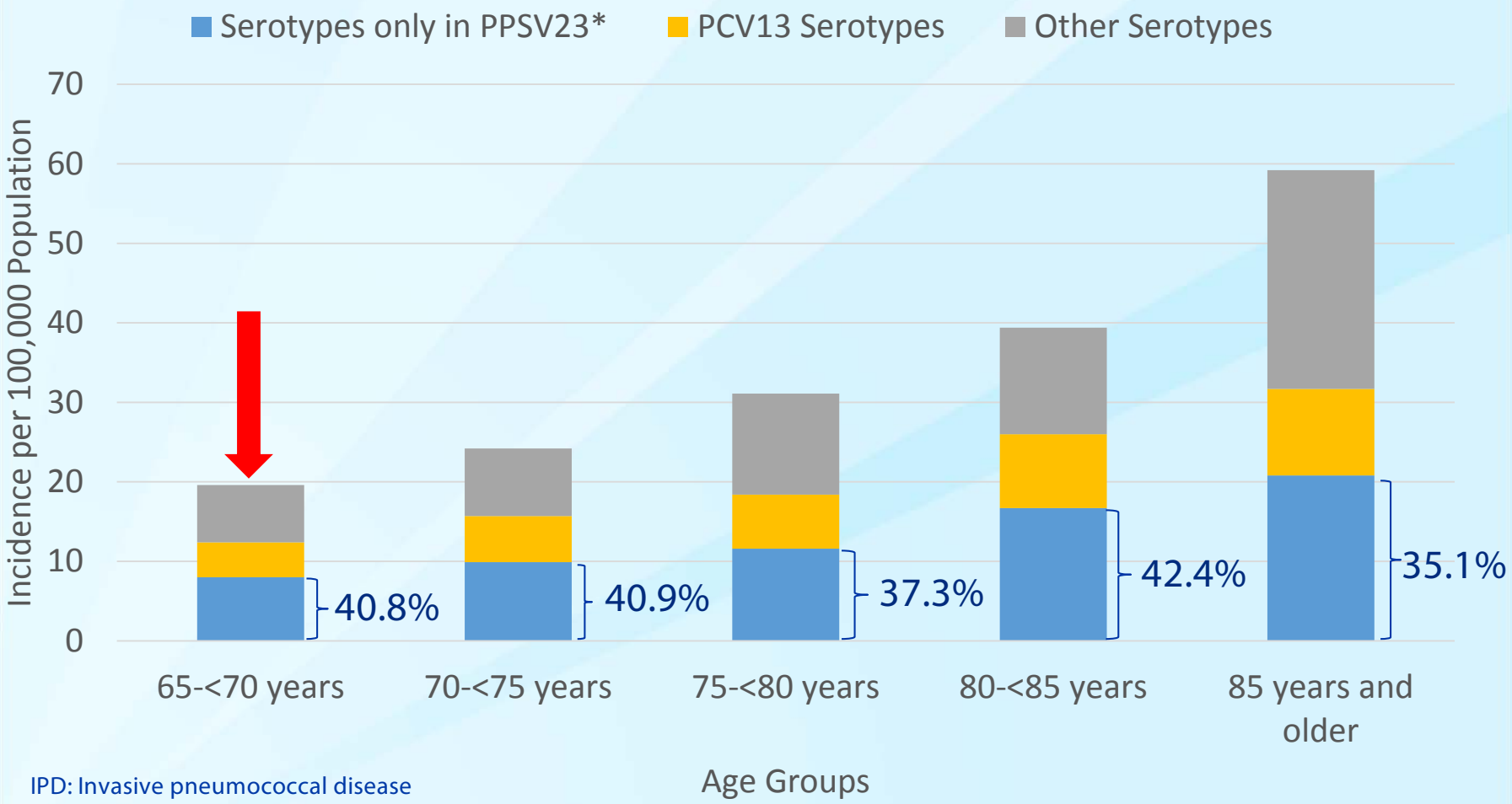
- **None of the studies designed to identify optimal length of interval between PCV13 and PPSV23**
  - Comparisons across studies difficult to make
- **Intervals of 2[1], 6[1-5], 12[6,7] months, and 3–4[8] years**
  - Longer interval between PCV and PPSV23 (≥1 year) may improve the response
  - Increased reactogenicity suggested with shorter (2 months) interval[1]

1. Miernyk, CID 2008; 2. Musher, JID 2008; 3. Goldblatt, CID 2009; 4. Lazarus, CID 2011; 5. MacIntyre, PLOS ONE 2014; 6. Greenberg, Vaccine 2014; 7. de Roux, CID 2008; 8. Jackson, Vaccine 2013

Considerations for Harmonizing Intervals Among Adults Aged ≥65 Years

- Implementation and programmatic challenges
- Immunogenicity studies
- Risk window for PPSV23-only serotypes

Annual Incidence of IPD by Serotype Group and Age Group, ABCs 2013



IPD: Invasive pneumococcal disease

ABCs: Active Bacterial Core Surveillance

*Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F

Conclusions

- **Changing the PCV13 → PPSV23 interval from 6–12 months to ≥1 year for adults aged ≥65 years would be appropriate**
  - Pros:
    - Harmonizing with the interval between PPSV23→ PCV13
    - Consistent with current CMS policy
    - Immune response may be improved
  - Cons:
    - Increase in risk window for IPD caused by PPSV23-only serotypes from currently recommended 6–12 months to ≥1 year

Current and Proposed Intervals Between PCV13 → PPSV23

Age groups	Underlying conditions	Interval Recommendations	
		Current	Proposed
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	No change
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	No change
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	No change
≥65 years	NA	6–12 months (minimum 8 weeks)	≥1 year

September 19, 2014 / 63(37);822-825; October 12, 2012, Vol 61, #40; June 28, 2013 / 62(25);521-524; December 10, 2010 / 59(RR11);1
18 June 28, 2013 / 62(25):521-524

QUESTIONS?

HARMONIZING INTERVALS FOR PPSV23 → PCV13

Currently Recommended Intervals Between PPSV23 → PCV13

Age groups	Underlying Conditions	Current interval recommendations
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥1 year
≥65 years	NA	≥1 year

September 19, 2014 / 63(37);822-825; October 12, 2012, Vol 61, #40; June 28, 2013 / 62(25);521-524; December 10, 2010 / 59(RR11);1-18

Current and Proposed Intervals Between PPSV23 → PCV13

Age groups	Underlying Conditions	Interval Recommendations	
		Current	Proposed
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	?
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	?
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥1 year	No Change
≥65 years	NA	≥1 year	No Change

September 19, 2014 / 63(37);822-825; October 12, 2012, Vol 61, #40; June 28, 2013 / 62(25);521-524; December 10, 2010 / 59(RR11);1-18

Considerations for Harmonizing Intervals of PPSV23 → PCV13

- The proportion of children potentially affected by this recommendation
- Programmatic issues/practical aspects
- Immunogenicity studies

Groups of Children for Whom This Recommendation May Be Applicable

- Children who were aged ≥2 years and indicated to receive PPSV23 before PCV7 became available in 2000 (current cohort of 17–18 year olds)

- Children with underlying conditions who did not receive any PCV13 or received incomplete PCV13 series as infants, and have already received a dose of PPSV23

Considerations for Harmonizing Intervals of PPSV23 → PCV13

- The proportion of children potentially affected by this recommendation
- Programmatic issues/practical aspects
- Immunogenicity studies

Current and Proposed Intervals for Children 2–18 Years with Underlying Conditions

Age groups	PCV13→ PPSV23	PPSV23→ PCV13
24–71 mo	≥8 weeks	≥8 weeks ↓ ≥1 year
6–18 years	≥8 weeks	≥8 weeks ↓ ≥1 year

Proposed Intervals for Groups with Underlying Conditions

Age groups	PCV13→ PPSV23	PPSV23→ PCV13
24–71 mo	≥8 weeks	≥1 year
6–18 years	≥8 weeks	≥1 year
≥19 years	≥8 weeks	≥1 year

Considerations for Harmonizing Intervals of PPSV23 → PCV13

- The proportion of children potentially affected by this recommendation
- Programmatic issues/practical aspects
- Immunogenicity studies

Does Evidence Support the Change of the Interval for PPSV23 → PCV13 Series to ≥1 Year for Children 2–18 Years with Underlying Conditions?

- Limited data from immunogenicity studies available
- Data suggesting blunting of immune response to PCV when interval <1 year after PPSV23 in adults[1-7]
  - Interval of ≥1 year recommended for adults
- Reviewed immunogenicity studies comparing:
  - PPSV23 → PCV7 vs. PCV7 (comparison not available for PCV13)
  - Single-arm study on response to PCV13 in children with sickle cell disease who have received PPSV23 (no comparison group)

1Lazarus, CID 2011; 2 Musher, JID 2008; 3 de Roux, CID, 2008; 4 Jackson, Vaccine, 2013; 5 Greenberg,Vaccine 2014; 6 Crum-Cianflone, JID 2010; 7 Miiro, JID 2005

Summary of Immunogenicity Studies Comparing PPSV23 → PCV7 vs. PCV7 in Children

Interval	Difference in immune response after PPSV23 → PCV7 compared to single PCV7 dose
1 year	Equivalent or greater (6/7 serotypes)*[1,2]
18–39 months	Equivalent (3/4 serotypes) or lower (1/4 serotype)**[3]
5.2 ± 3.4 years	Equivalent (7/7 serotypes)[4]

[1] Blum, Vaccine 2000

[2] O'Brien, Lancet Infect Dis 2007

[3] Spoulou, Vaccine 2005

[4] Mikoluc, Eur J Clin Microbiol Infec Dis 2008

*No statistical comparison available. Study was done among healthy children.

** HIV-positive children compared with healthy controls.

Immunogenicity Study Result from a Single-arm Study

- **Target population:**
  - Children 6 to <18 years with sickle cell disease with history of PPSV23 ≥ 6 months before enrollment
    - Median time since PPSV23: 2.9 years (range 6 mo–11.8 years)
- **Intervention (single-arm study):**
  - PCV13 administration
- **Outcome measurements:**
  - IgG concentrations and OPA 1 month after PCV13 dose
- **Results:**
  - Able to mount statistically significantly higher immune response post-PCV13 vs. pre-vaccine
  - No correlation between time since last PPSV23 and response to PCV13

1. Montalembert, Pediatr Blood Cancer 2015

Summary of Evidence

- No studies designed to evaluate the length for an optimal interval between PPSV23 and PCV13
- No clear evidence of blunting of immune response when PPSV23 is given before PCV vs. PCV alone
  - Intervals evaluated: 1 year[1], 18–39 months[2], 5 years[3]
- Single-arm study suggests no correlation between time since last PPSV23 and response to PCV13
  - Median time since PPSV23: 2.9 years (range 6 mo–11.8 years)

1 Blum 2000 Vaccine; 2 Spoulou, Vaccine 2005;3 Mikoluc, Eur J Clin Microbiol Infec Dis 2008; 4. Montalembert, Pediatr Blood Cancer 2015

Conclusions

- **Changing the PPSV23 → PCV13 interval from ⩾8 weeks to ⩾1 year for children 2–18 years with underlying conditions would be appropriate**
  - Pros:
    - Harmonization across all age groups with underlying conditions
    - Proportion of children affected by the change is small
    - Avoid potential blunting of response to PCV13
  - Cons:
    - Interval will be different from the recommended interval for PCV13 → PPSV23 for the same age group (≥8 weeks)

Current and Proposed Intervals Between PPSV23 → PCV13

Age groups	Underlying Conditions	Interval Recommendations	
		Current	Proposed
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥1 year	No Change
≥65 years	NA	≥1 year	No Change

September 19, 2014 / 63(37);822-825; October 12, 2012, Vol 61, #40; June 28, 2013 / 62(25);521-524; December 10, 2010 / 59(RR11);1-18

Intervals Between the Two Pneumococcal Vaccines Incorporating the Proposed Changes

Age groups	Underlying conditions	PCV13→ PPSV23	PPSV23→ PCV13
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
≥65 years	NA	≥1 year	≥1 year

September 19, 2014 / 63(37);822-825; October 12, 2012, Vol 61, #40; June 28, 2013 / 62(25);521-524; December 10, 2010 / 59(RR11);1
18 June 28, 2013 / 62(25):521-524

QUESTIONS?

Proposed changes for ACIP Vote

Current Recommendations for Intervals Between PCV13 Followed by PPSV23 Among Adults ⩾65 Years of Age

- The dose of PPSV23 should be given **6 –12 months** after a dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit. The two vaccines should not be coadministered, and the minimum acceptable interval between PCV13 and PPSV23 is **8 weeks.**

MMWR Sep 2014, Vol. 63, No. 37

Adults ≥65 years of Age with No Previous Pneumococcal Vaccine (PCV13 or PPSV23)

Proposed guidance on intervals for sequential use of PCV13 followed by PPSV23:

A dose of PPSV23 should be given at least 1year following a dose of PCV13. The two vaccines should not be co-administered. If a dose of PPSV23 is given earlier than the recommended interval, the dose need not be repeated.

Current Recommendations for Interval Between PPSV23 Followed by PCV13 Among Children 2–18 Years with Underlying Conditions

Infants and young children <6 years:

- History of complete PCV7 vaccination
  - For children who have underlying medical conditions, a single supplemental PCV13 dose is recommended through 71 months. This includes children who have received PPSV23 previously. PCV13 should be administered **at least 8 weeks** after the most recent dose of PCV7 or PPSV23.

MMWR December 10, 2010

Current Recommendations for Interval Between PPSV23 Followed by PCV13 Among Children 2–18 Years with Underlying Conditions

Children 6–18 years:

- Children aged 6–18 years who have not received PCV13 and are at increased risk for IPD because of anatomic or functional asplenia, including SCD, HIV infection, CSF leaks, cochlear implants, or other immunocompromising conditions; and who previously received ≥1 doses of PPSV23 should be given a single PCV13 dose ≥8 weeks after the last PPSV23 dose, even if they have received PCV7

MMWR June 28, 2013

Children 2–18 years with Underlying Conditions

Proposed guidance on intervals for sequential use of PPSV23 followed by PCV13:

A dose of PCV13 should be given at least 1year following a dose of PPSV23. The two vaccines should not be co-administered. If a dose of PCV13 is given earlier than the recommended interval, the dose need not be repeated.

ACIP Vote

Adults ≥65 years of Age with No Previous Pneumococcal Vaccine (PCV13 or PPSV23)

Proposed guidance on intervals for sequential use of PCV13 followed by PPSV23:

A dose of PPSV23 should be given at least 1year following a dose of PCV13. The two vaccines should not be co-administered. If a dose of PPSV23 is inadvertently given earlier than the recommended interval, the dose need not be repeated.