Pneumococcal Vaccines for Older Adults: What is the right approach?

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My background and funding

- US Centers for Disease Control and Prevention (CDC), retired July 1

- Current funding:
  - IHRC, Inc.: consultant for CDC
  - Limited-time consulting: Guidepoint, SutroVax, Inc
Pneumococcal vaccines for older adults
What is the right approach?

- Background -- why the need for vaccines for adults
- Considerations and reconsiderations for using conjugate vaccine-- the US experience
- What do we want from a pneumococcal vaccine for adults?
Colonization, Mucosal Disease, Invasive Disease

Figure 1. Pathogenic route for S. pneumoniae infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.

Bogaert, Lancet Infect Dis 2004;4:144-54
Colonization, Mucosal Disease, Invasive Disease

Transmission

Mucosal Disease
- Pneumonia
- Otitis media
- Sinusitis

Invasive Disease
- Empyema
- Septicaemia
- Peritonitis
- Arthritis/osteomyelitis
- Meningitis

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Bogaert, Lancet Infect Dis 2004;4:144-54
Age-Specific Incidence of Invasive Pneumococcal Disease, US, 1998

I've been calling you all day.

That's a calculator.
Vaccines to Preserve Health

- People age 65+ years a large and growing segment of the population
- Many are healthy, active, engaged
- Immunizations a simple way to preserve health

Photo source: dailymail.co.uk from Reddit
Vaccinating children highly effective for preventing disease in adults

Moore, IDSA, 2009
Need better prevention measures for pneumonia in older adults

• Prevention measures targeting respiratory infections
  – Indirect effects from pediatric PCV program
  – 23-valent pneumococcal polysaccharide vaccine (PPSV23) used in US since 1983
  – Expanded flu vaccine recommendations and improved coverage
  – Smoking cessation and prevention program; second-hand smoke restricted in public areas

• In spite of these measures:
  – Pneumonia/influenza still 8th leading cause of death in US
  – >57,000 deaths in 2015 CDC.gov
### Polysaccharide & Conjugate Vaccines: A Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Polysaccharide</th>
<th>Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>Purified polysaccharide</td>
<td>Purified polysaccharide covalently bound to carrier protein</td>
</tr>
<tr>
<td>Immunogenic?</td>
<td>Only among &gt;2 year-olds</td>
<td>All ages (T-dependant pathway)</td>
</tr>
<tr>
<td>Number of serotypes</td>
<td>4→14→23</td>
<td>7→10→13</td>
</tr>
<tr>
<td>Effect against bacteremia</td>
<td>Substantial</td>
<td>Substantial</td>
</tr>
<tr>
<td>Effect against carriage</td>
<td>None</td>
<td>Substantial</td>
</tr>
<tr>
<td>Effect against non-bacteremic pneumonia</td>
<td>No consensus</td>
<td>Moderate</td>
</tr>
<tr>
<td>Schedule</td>
<td>≤3 doses after age 2 years</td>
<td>4 doses &lt;age 2 years; possibly 1 after</td>
</tr>
<tr>
<td>Cost</td>
<td>US $55</td>
<td>US $124</td>
</tr>
<tr>
<td>Examples</td>
<td>23-valent Pneumococcal Polysaccharide Vaccine (PPSV23)</td>
<td>13-Valent Pneumococcal Conjugate Vaccines (PCV13)</td>
</tr>
</tbody>
</table>
ACIP Pneumococcal Work Group Activities 2010-2014

Routine recs for infants and children; permissive recs for 6-18 years olds with IC

Deferred routine recs for adults pending results of CAPITA and indirect effects

Recommendations for adults with immunocompromising conditions (IC)

Recommendations for 6-18 years olds with IC

Feb 2010
Dec 2011
Feb 2012
Jun 2012
Jan 2013
Feb 2013
Aug 2014

PCV13 licensed (replaced PCV7)
PCV13 licensed for adults ≥50 years old
PCV13 licensed for children 6-17 years old

IC = with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants

PCV13 for adults 65 years and older?
Considerations for changing vaccine policy

Evidence base

GRADE

Policy/statute considerations

Economic considerations

PCV13 for all adults 65+?

Safety

Programmatic considerations

Communication challenges

Equity

Acceptability
• Randomized, placebo-controlled trial of 84,496 adults ≥65yrs of age in the Netherlands

• Primary endpoint
  • Vaccine-type community-acquired pneumonia
  • Measured using serotype-specific urine antigen assay
CAPiTA: Cumulative Episodes of Efficacy End Points in the Per-Protocol Population

**A** Vaccine-Type CAP

- **Placebo**
- **PCV13**

**B** Vaccine-Type IPD

- **Placebo**
- **PCV13**

**CAP vaccine efficacy 46% (22%, 63%)**

**IPD vaccine efficacy 75% (41%, 91%)**

# PCV in Older Adults: Quality of evidence (GRADE)

<table>
<thead>
<tr>
<th>Comparison</th>
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<th>Study Design (# studies)</th>
<th>Findings</th>
<th>Quality of evidence</th>
<th>Overall evidence type</th>
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<td>PCV13 vs. no vaccination</td>
<td>IPD</td>
<td>RCT (1)</td>
<td>Decreased risk among vaccinated</td>
<td>2</td>
<td>2</td>
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<td>PCV13 vs. no vaccination</td>
<td>Pneumonia</td>
<td>RCT (1)</td>
<td>Decreased risk among vaccinated</td>
<td>1</td>
<td>2</td>
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<tr>
<td>PCV7 or PCV13 vs. PPSV23</td>
<td>Immunogenicity</td>
<td>RCT (6)</td>
<td>Response improved for PCV vs. PPSV23 or no difference</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PCV13 vs. PPSV23</td>
<td>Serious and systemic adverse events</td>
<td>RCT (3)</td>
<td>No difference or decreased risk with PCV13</td>
<td>1</td>
<td>1</td>
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OK, the vaccine works…

…but do we need it?
“We don’t need PCV13 because vaccinating children has taken care of virtually all the disease.”

Q: Disease rates have gone down…but have they gone down so far that vaccinating adults is pointless?

A: Need to do the math!
Modeling expected public health impact and cost-effectiveness of PCV13 for older adults in the U.S.

- Various strategies considered:
  - Vaccination at ages 50, 60, and 65 years
  - PCV13 instead of PPSV23
  - PCV13 in sequence with PPSV23

- Took into account:
  - Anticipated reductions in vaccine-serotype disease over time because of pediatric program (used PCV7 experience)
  - A guess at how quickly coverage would increase
  - Waning immunity over time after vaccination
  - Disease occurring only in nonimmunosuppressed persons
  - A lot of other stuff

Expected public health impact and cost-effectiveness in the U.S.

- Adding PCV13 at age 65 years to existing PPSV23 recommendations likely the optimal strategy
  - PPSV23’s extended serotype range helps with IPD; PCV13 helps with pneumonia
- Health benefits for cohort of 65-yo’s vaccinated
  - 5000 fewer pneumonia hospitalizations
  - 7300 fewer outpatient pneumonias
- Cost-effectiveness comparable to other accepted adult interventions (base case: $62,000/QALY)
- But, cost-effectiveness likely to decrease over time
  - For 2019 cohort, $273,000/QALY

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Caveats:
- Need for PCV likely to drop over time
- US situation may not be applicable elsewhere

Considerations for changing vaccine policy

- **Evidence base**
- **GRADE**
- **Safety**
- **Programmatic considerations**
- **Equity**
  - Acceptability
  - Communication challenges

- **PCV13 for all adults 65+?**

- **Policy/statute considerations**
- **Economic considerations**

- **Acceptability**
- **Communication challenges**
- **Equity**
Considerations for changing vaccine policy

PCV13 for all adults 65+?

Evidence base

GRADE

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Acceptability

Communication challenges

VOTE: YES 13

NO 2
2014 Advisory Committee on Immunization Practices (ACIP)

- Both PCV13 and PPSV23 should be routinely administered in series to all adults aged ≥65 years.
- When possible, PCV13 given first followed by PPSV23 later
- The recommendations for routine PCV13 use among adults aged ≥65 years will be reevaluated in 2018 and revised as needed.

2015 update: interval between PCV13 and PPSV doses should be ≥ 1 year (regardless of order)

Tomczyk S et al. MMWR September 19, 2014 / 63(37);822-825
Kobayashi M et al. MMWR September 4, 2015 / 64(34);944-947
Mandate to:

- Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines
- Assess recommendations considering up-to-date evidence and evidence strength
- Revise or update recommendations for pneumococcal vaccine use, as needed

Setting:

- PCV13 coverage modest
  - Increased to ~40% through 2017 among adults 65+ yrs
  - Lower among those 19-64 yrs with vaccine indications
- Safety assessment good
  - VAERS: mostly injection site reactions, no unexpected reports or patterns
  - VSDL: no increased risk of reactions compared to PPSV23

Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance

Drops in most vaccine types
No change in serotype 3 burden
Minimal/no replacement

Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance
Evidence for ACIP’s assessment of Adult PCV13 policy: Invasive disease

- PCV13-type IPD incidence in US adults ≥65 years old declined 68% after pediatric PCV13 began in 2010; no change from 2014 to 2016
  - PCV13 serotype 3 most common serotype
  - Low PCV13 disease rates among Alaska Natives and Navajo before implementation of adult program (indirect effects); no change after

- Mathematical model estimated direct PCV13 effects on observed IPD trends in IPD among adults ≥65 years old
  - Between 80-760 IPD cases prevented since 2014 among U.S adults ≥65 years; benefits decreasing over time

- PCV13 effectiveness against PCV13-type IPD 47% (95%CI 4–71%) to 65% (95%CI 19–85%) in 2 case-control studies
  - Confidence intervals overlap with the CAPiTA PCV13

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Pillishvili, ACIP meeting Feb 2018; Hammitt, ACIP June 2018
Evidence for ACIP’s assessment of Adult PCV13 policy:

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- PCV13 effectiveness against PCV13-type IPD 47% (95%CI 4–71%) to 65% (95%CI 19–85%) in 2 case-control studies
  - Confidence intervals overlap with the CA PiTA PCV13 efficacy estimates of 75% (95%CI 41–91%)
- PCV13 effective in older adults (serotype 3?)
- Direct benefit of adult program small in most recent years

Pillishvili, ACIP meeting Feb 2018; Hammitt, ACIP June 2018

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54
Evidence for ACIP’s assessment of Adult PCV13 policy: Pneumonia

- PCV13 effectiveness against PCV13-type pneumonia 73% (95% CI 13–92) demonstrated in a test negative case-control study design
  - Confidence intervals overlap with CAPiTA PCV13 efficacy estimates of 45% (95%CI 14–65%) against PCV13-type pneumonia

- Among American Indians in the southwest US, 26% of chest x-ray confirmed pneumonia had pneumococcal diagnosis; of these, 31% PCV13-types by SSUAD, mostly serotype 3

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

McLaughlin, ACIP Feb 2018; Hammitt, ACIP June 2019
Evidence for ACIP’s assessment of Adult PCV13 policy:

**Pneumonia**

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- Among American Indians in the southwest US, 26% of chest x-ray confirmed pneumonia had pneumococcal

- **PCV13 effective against pneumonia (serotype 3?)**
- **Remaining pneumonia mostly nonvaccine types or serotype 3**

McLaughlin, ACIP Feb 2018; Hammit, ACIP June 2019
Evidence for ACIP’s assessment of Adult PCV13 policy: Nasopharyngeal Carriage

- Nasopharyngeal carriage before and after PCV13 introduction in adults ≥65 in Atlanta
  - Children <5 years:
    - PCV13-serotype carriage declined from 8% in 2011 to <1% in 2017
    - Total *S. pneumoniae* carriage remained the same (~30%)
  - Adults ≥65 years:
    - PCV13-serotype carriage 0.2% in 2015-16
    - Total *S. pneumoniae* carriage also low (1.8%)

Thomas, ACIP meeting Oct 2017; Lessa, ACIP meeting Oct 2017

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54
Evidence for ACIP’s assessment of Adult PCV13 policy:

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Older adults rarely exposed to PCV13 serotypes

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54
ACIP Meetings coming soon

- October 2018: Discussion and data review
  - PCV13 impact on IPD and serotype distribution for the remaining disease burden
  - U.S. trends in US pneumonia hospitalizations, noninvasive pneumococcal pneumonia in ABCs sites for older adults
  - Cost effectiveness of PCV13 for adults ≥65 year old
  - Preliminary EtR and GRADE

- February 2019: Tentative vote
  - Should PCV13 be administered routinely to all adults aged ≥65 years in a setting of sustained PCV13 indirect effects?
Goal: develop a uniform approach to evaluation and use of the evidence base for ACIP recommendations

Framework:

- Statement of problem
  - Public health priority
  - Burden of disease
- Benefits and harms (GRADE)
  - Balance of desirable and undesirable effects
  - Certainty in evidence
  - Values and preferences of target population
- Acceptability to stakeholders
- Resource use
  - Health economic analyses
- Feasibility
  - Implementation considerations
ACIP PCV13 recommendations for adults: To drop or not to drop?

- **DROP PCV13 FOR OLDER ADULTS**
  - Disease caused by vaccine types now uncommon, except serotype 3
  - Preliminary evidence suggests herd effects from children drive low rates in adults, not direct effects
  - Vaccination is a lot of time and expense for low likelihood of benefit

- **DON’T DROP**
  - Vaccine is safe and effective
  - Communication/acceptability challenges, i.e. “Drop the more effective vaccine?”
  - Logistics/systems challenges: If new vaccines around the corner, why not wait to change and avoid rapid program shifts?
What serotypes would we include in the ideal adult pneumococcal conjugate vaccine?
Top serotypes causing IPD in US adults 65+ years, 2016/17

What about a different adult PCV?
- PCV13 serotypes – 6.1 cases/100K
- PPSV23 serotypes – 13.5 cases/100K
- 10 top serotypes (2 PCV13 +8 new) -- 14.7/100K

Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance
Top serotypes causing IPD in US and UK adults 65+ years, 2016/17

Sources: US CDC Active Bacterial Core surveillance; Ladhani et al Lancet Infect Dis 2018
Considerations for designing an adult vaccine

• Serotype 3 remains common, even with recs for PCV13 (U.S.) and PPV23; differs from other PCV antigens. Is a better serotype 3 component possible?
• In push to cover more serotypes, potentially to replace PPSV23, will individual components interfere with each other’s ability to elicit an immune response?
• Given herd effects, should adult vaccines target different serotypes than those in the pediatric formulation? Or would production/licensing issues preclude this option?
• Will costs permit use in low- and middle-income countries?
• How to chose best serotypes to include, given differences between countries? 8-10 antigens likely to target substantial burden
Questions

What should ACIP do about the adult recommendation?

What/how many serotypes should an adult vaccine have?

Photo source: nowthatsnifty.blogspot.com